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Physical Activity in the Elderly and Orthopaedic Surgery

Edited by
Rocco Papalia, Vincenzo Denaro, Fabio Pigozzi and
Chiara Fossati

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Physical Activity in the Elderly and Orthopaedic Surgery

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About the Editors

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Editorial

Elderly or ageless? Physical Activity in the Aged Orthopaedic Patient

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Progression of osteoarthritis in the elderly is often a synonym of impaired function, discontinuation of physical activity and sport participation [1]. However, there is consistent evidence suggesting that the role of sports activity is of paramount importance in the whole natural history of osteoarthritis, as well as of degenerative disc disease. This contrast should be promptly faced by the orthopaedic surgeon, gerontologist and sports physician, to avoid early impairment or discontinuation of patient’s activity. In fact, apart from preventing the onset of major symptoms and delaying the loss of function as primary and secondary prevention, exercise is extremely important to improving muscular conditioning and strength before surgery and for the post-operative recovery and rehabilitation.

According to the World Health Organization, the concept of physical activity refers to several entities, including light individual exercise, collective training, individual or team sports participation [2]. All of these activities have specific effects on the whole organism and allow the human body to remain healthy not only for musculoskeletal fitness but also for the improvement of cardiovascular, metabolic and psychosocial status. If this is especially true for young people, the elderly become ageless if they are able to stay fit, to stay healthy and to maintain the physical and mental fitness that allow them to face organ deterioration, functional impairment and possible major surgeries. From an economical and occupational perspective, it is worth underlining that, given the increased retirement age of citizens in Europe, preserving a good to excellent functional status is of paramount importance to improving productivity and avoiding early retirement and inability to work [3]. All of these features are enclosed within the framework of successful ageing, according to which the organism deterioration follows an ordered pathway to avoid patient discomfort and disability [4].

Therefore, physical activity represents complementary therapeutics for the management of osteoarthritis and for other musculoskeletal degenerative diseases. A special focus of international research concerns the involvement of older patient in exercise programs as a conservative treatment, but also in the preoperative setting, to improve surgical outcomes [5]. It is a common experience for the orthopaedic surgeon that a fit patient has a faster and better recovery after a major surgical procedure, including joint arthroplasty, and next to clinical experience, the literature evidence is growing, reporting significant improvement of patient-reported outcomes either for pain or for function [6].

The aim of the present Special Issue is to collect the available evidence concerning the role of physical activity as a conservative treatment for large joint osteoarthritis and low back pain, and as prehabilitation and rehabilitation, before and after arthroplasty surgery. A systematic approach has been followed for evidence collection, and a meta-analytic methodology has been advocated in most of the papers, to ensure a comprehensive assessment of available data.

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Review

Common Musculoskeletal Disorders in the Elderly: The Star Triad

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Abstract: Musculoskeletal disorders are debilitating conditions that significantly impair the state of health, especially in elderly subjects. A pathological triad of inter-related disorders that are highly prevalent in the elderly consists of the following main “components”: sarcopenia, tendinopathies, and arthritis. The aim of this review is to critically appraise the literature relative to the different disorders of this triad, in order to highlight the pathophysiological common denominator and propose strategies for personalized clinical management of patients presenting with this combination of musculoskeletal disorders. Their pathophysiological common denominator is represented by progressive loss of (focal or generalized) neuromuscular performance with a risk of adverse outcomes such as pain, mobility disorders, increased risk of falls and fractures, and impaired ability or disability to perform activities of daily living. The precise management of these disorders requires not only the use of available tools and recently proposed operational definitions, but also the development of new tools and approaches for prediction, diagnosis, monitoring, and prognosis of the three disorders and their combination.

Keywords: aging; osteoarthritis; sarcopenia; tendinopathies

1. Introduction

Musculoskeletal disorders are debilitating conditions that significantly impair the state of health, especially in elderly subjects, since they are associated with pain, mobility disorders, increased risk of falls and fractures, and impaired ability or disability to perform activities of daily living. A pathological triad of inter-related disorders that are highly prevalent in elderly subjects consists of the following main “components”: sarcopenia, tendinopathies, and arthritis (the acronym “STAR” will be henceforth adopted).

Interdependency within the different components of the triad fuels an accelerating disease progression that culminates in motor impairment, reduced quality of life, and increased risks of disability, morbidity, and mortality. Clinical and experimental findings show the interdependency within the three disorders. In fact, quadriceps weakness increases the risk of knee and hip osteoarthritis and also increases disease- and treatment-related complications [1,2]. Similarly, poor abductor hip function and low physical performance are known risk factors for gluteal tendinopathy [3,4]. Recent studies also showed that motor impairments (that are common in patients with both lower limb tendinopathies and hip or knee osteoarthritis) may predispose to sarcopenia and contribute to its progression [5]. Furthermore, age-related comorbidities, such as chronic obstructive pulmonary disease and congestive heart failure, can limit mobility resulting in decreased muscle and tendon function, thus propagating changes already occurring in the musculoskeletal system [6]. Although common pathways

have been implicated in the pathogenesis of the different components of the triad [6], these diseases are rarely evaluated in a comprehensive manner [6] and, to the best of our knowledge, no previous study has investigated the frequency of comorbidity of sarcopenia, tendinopathies, and arthritis.

An example of a clinical case that is commonly seen in daily practice, highlighting the possible interdependency of the STAR triad's musculoskeletal disorders is as follows. A 70-year-old female presents to her general practitioner with complaints of difficulty in moving and pain. She reports that it is becoming difficult to rise from a chair and she sometimes loses her balance when walking on uneven surfaces. Reaching cups on the high kitchen shelves causes shoulder pain, and her knees, which used to ache only in the morning, now hurt all the time. Though she had multiple minor musculoskeletal injuries in her youth and worked in a factory for twenty years, she had only a few medical concerns during adulthood. After she retired, however, her activity level declined, and controlling her weight gain and diabetes has been difficult. Her doctor is concerned that multiple musculoskeletal disorders are affecting her independence and quality of life.

The aim of this narrative review is to critically appraise the literature relative to the different disorders of this "STAR" triad, in order to highlight the pathophysiological common denominators and propose strategies for personalized clinical management of patients presenting with this combination of musculoskeletal disorders. Literature research was performed, including all relevant studies up to January 2020 by searching the Medline/PubMed database and Web of Science using the following search terms: arthritis, muscle weakness, musculoskeletal pain, osteoarthritis, physical frailty, sarcopenia, tendinopathy, tendon injury, and healing.

2. Sarcopenia

2.1. Definition

Sarcopenia is the loss of skeletal muscle mass and function that occurs during the aging process (primary sarcopenia) or due to the presence of an underlying disease or medication (secondary sarcopenia). While secondary sarcopenia relies on the diagnosis and treatment for the underlying causation, primary sarcopenia has been more challenging to characterize. The European Working Group on Sarcopenia in Older People described sarcopenia as "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death" [7].

2.2. Epidemiology

Epidemiological studies showed that from the second to the eighth decade of life, whole body and appendicular lean mass decline by about 20% in men and 30% in women [8,9]. Sarcopenia, therefore, is prevalent in older adults, especially women, and presents substantial variations depending on age and geographic area. A 2014 systematic review reported the following sarcopenia prevalence data within different healthcare settings: 1%–29% in the community, 10% in acute hospital care, and 14%–33% in long-term care setting [10].

2.3. Pathophysiology

From a pathophysiologic perspective, sarcopenia can be considered as an organ failure: Correa-de-Araujo and Hadley [11] proposed the concept of "skeletal muscle function deficit", while Marzetti et al. [12] proposed the pathophysiologic construct of "muscle insufficiency".

This organ failure can develop chronically (more often) or acutely (e.g., during immobilization) and results from a combination of neural and muscular adaptations [13,14]. The former adaptations consist of neuropathic processes leading to motor unit denervation and preferential loss of fast motor units. The latter adaptations consist of a loss of muscle mass that is due to a decrease in muscle fiber number (hypoplasia) and size (atrophy), which particularly affects type 2 fibers (that are more vulnerable to atrophy than type 1 fibers). Given the abovementioned preferential loss of fast motor

units (containing fast type 2 fibers), the muscular adaptations could also imply a fast-to-slow transition of fiber types (i.e., a change of the myosin heavy chain (MHC) isoform expression toward the slower phenotype) [13]. However, MHC expression is also affected by the level of neuromuscular activity: disuse favors the expression of fast MHC isoforms, while physical activity leads to either a fast-to-slow (glycolytic-to-oxidative) phenotype transition or a shift toward the slower population of fast fibers (i.e., a bidirectional transformation from MHC-1 and MHC-2X isoforms toward MHC-2A isoform) [13–15]. This variability in muscle adaptations to physical activity is a function of the pre-training MHC phenotype, training history, and training type. Hence, an MHC phenotype characteristic of aging does not exist since it is the result of the complex interaction between age-related neurodegenerative changes and physical activity status, which varies across different individuals.

2.4. Clinical Presentation

The European Working Group on Sarcopenia in Older People proposed in 2010 an operational definition of sarcopenia based on the co-occurrence of low muscle mass and low muscle function (strength or performance) [7]. This operational definition has recently been updated as follows: (1) low muscle strength is identified as a key characteristic and a primary indicator of probable sarcopenia; (2) sarcopenia diagnosis is confirmed by the presence of low muscle quantity or quality; and (3) detection of low physical performance predicts adverse outcomes, so such measures are thus used to identify the severity of sarcopenia. Therefore, when low muscle strength, low muscle quantity/quality, and low physical performance are all detected, sarcopenia is considered to be severe [16].

Other consensus groups (International Working Group on Sarcopenia (IWGS), Society of Sarcopenia, Cachexia and Wasting Disorders (SSCWD), Foundation for the National Institutes of Health Sarcopenia Project, and Asian Working Group on Sarcopenia) agree that the diagnosis of sarcopenia should incorporate a muscle mass evaluation with the assessment of strength and/or physical performance [17–20].

Therefore, the reduction in muscle size and strength and neuromuscular performance impairment must be considered as core clinical presentations of sarcopenia: a critical mass of these phenotypic components identifies and evaluates the severity of the syndrome. This operationalization of the sarcopenic syndrome resembles the definition of the frailty phenotype previously proposed by Fried et al. [21] that is based on the co-occurrence of (three or more of) the following criteria: unintentional weight loss, self-reported exhaustion, muscle weakness (low grip strength), slow walking speed, and low physical activity. Most of these criteria are the same required for the diagnosis of sarcopenia. Consistently, sarcopenia must be considered as a key component of frailty [22].

In addition to the formal clinical presentation framework, a recent stated-preference study performed in community dwelling, elderly, sarcopenic patients provided insights on the clinical features of sarcopenia that are relevant from the patients' perspective, including mobility impairment, inability to manage domestic activities, increased risk of falls, fatigue, and reduced quality of life [23].

Therefore, treatment interventions for sarcopenic patients should be performed to address not only the core phenotypic components of the syndrome (the impairments of muscle mass and function), but also the associated negative health outcomes.

2.5. Management

Understanding the pathophysiology and core clinical characteristics of sarcopenia is key to developing effective interventions, and translational research in this area is rapidly increasing [24]. Current management strategies include non-pharmacological and pharmacological approaches. Physical exercise, alone or in combination with nutritional interventions, is the non-pharmacological approach currently recommended as the primary treatment of sarcopenia [25]. In fact, physical exercise, most notably high-intensity resistance training, improves the strength and mass of skeletal muscles and counteracts the age-related decline in muscle size and function [24–26]. It is, however, worth noting that the feasibility, sustainability, and safety of resistance training in individuals with sarcopenia deserve

further investigation [26], especially because high-intensity resistance exercises increase the risk of muscle and tendon injuries and can also produce post-exercise muscle soreness and persistent fatigue. These symptoms (that also represent the core clinical characteristics of overtraining syndrome) [27] should be avoided in elderly subjects as they can be associated with reduced motor performance, mood changes, and poor quality of life. As older individuals seem to prefer easy and accessible training regimens that are easy to perform in any setting, body weight-based exercise programs for strength training may be preferable to programs involving gym equipment [28]. Current recommendations for physical exercise prescription in sarcopenic and frail older people include a balanced program of both endurance and strength exercises, performed on a regular schedule [29,30].

The effects of exercise may be enhanced by a wide variety of other treatments, including patient education (patients must be instructed to progressively increase training load and to train at a high intensity) [26] and nutritional supplements providing an adequate intake of protein, vitamin D, antioxidant nutrients, and long-chain polyunsaturated fatty acids [31].

Furthermore, evidence for the benefits of different physical therapies in improving muscle strength and mass individually is compelling, and evidence for their benefit in sarcopenia is growing. For example, neuromuscular electrical stimulation (i.e., the application of high-intensity and intermittent electrical stimuli to the skin above the muscles, with the main objective to generate involuntary muscle contractions, most often in isometric tetanic conditions) [32], whole body vibration (i.e., the use of a vertical or rotary oscillating platform as an exercise stimulus, while the individual engages in sustained static positioning or dynamic movements) [33], and focal muscle vibration (i.e., the application of pneumatic stimuli to the skin above the muscles, with the main objective to stimulate cutaneous and subcutaneous receptors without triggering visible muscle contractions) [34] proved to be effective in sarcopenic patients. However, the heterogeneity of the data regarding the adopted stimulation paradigms and training protocols does not yet allow firm conclusions to guide clinical recommendations for physical therapy prescription in sarcopenic patients.

Regarding pharmacological approaches, it is worth highlighting that no drugs have been approved yet for the treatment of sarcopenia. A recent umbrella review of systematic reviews and meta-analyses reported that only vitamin D, especially in older women, and testosterone in older men with low testosterone levels and muscle weakness can be justified in daily clinical practice to improve muscle mass and function in sarcopenic patients [35].

3. Tendinopathies

3.1. Definition

Tendinopathy is a musculoskeletal disorder characterized by tendon pain during an activity, tendon swelling and localized tenderness upon palpation, and loss of function [36]. Different medical terms are frequently used to define this disorder [37] and this ambiguity reflects the controversy that surrounds pathogenesis of tendinopathy. The traditional assumption was that tendon injury may result from repetitive mechanical loads and subsequent inflammatory responses (hence the term “tendinitis”) [38]. However, histopathological findings were unable to consistently find “classical” inflammatory cells. Instead, light microscopy investigation of samples of pathological tendons showed collagen degeneration, increased mucoid ground substance, and increased tenocytes with myofibroblastic differentiation (tendon repair cells) [39]. For this reason, “tendinosis” became the preferred term over “tendinitis” to avoid the implication of inflammation. Modern molecular techniques, however, have clearly shown the increased presence of macrophages and mast cells in tendinopathic tissues [40]. Therefore, chronic, low-grade inflammation may still be part of the pathogenesis [41,42]. For all the reasons mentioned above, tendon experts recommend the use of “tendinopathy”, a term that does not imply the presence of a particular pathological or biochemical process [36,43,44].

3.2. Epidemiology

The most common tendinopathies in the elderly involve two tendons (i.e., subscapularis and supraspinatus) of the rotator cuff of the shoulder [45,46] and the gluteal tendons of the hip [47]. Rotator cuff tendinopathy prevalence in the elderly population ranges from 5% to 7% [45,46], and a recent study investigating tendinopathies in a Dutch general practice found gluteal tendinopathy to have the highest prevalence (4.22 per 1000 person years) and incidence (3.29 per 1000 person years) of all lower limb tendinopathies [48]. Therefore, the following sections will focus on the pathophysiology, clinical characteristics, and management strategies for degenerative rotator cuff tendinopathy and gluteal tendinopathy (also known as “greater trochanteric pain syndrome”).

3.3. Pathophysiology

Despite the progress achieved over the last decades, there is still great uncertainty over the factors causing this pathology and controlling its progression. A widely accepted concept for explaining the origin and development of tendinopathy is the generation of excessive tensile loads within the tendon over time. If a rapid increase in the magnitude, duration, or frequency of loading occurs, tensile strength might be exceeded locally causing a micro-injury. The mechanisms underlying the progression of this micro-injury are currently not established, but it has been hypothesized that repetitive overloading of the tendon may overwhelm the tissue’s healing capacity causing a more severe injury [43,44]. This concept identifies excessive tensile load to be the key factor in tendinopathy origin and development. However, a number of other findings indicated that there is more into the etiology and pathophysiology of tendinopathy than just excessive tensile load. For example, it has been shown in recent *in vivo* studies that human tendons may undergo non-uniform displacements during passive or active force application, with deeper tissue layers deforming more than superficial ones [49]. Therefore, not only excessive tensile stress, but also excessive compressive stress as well as “stress-shielding” (i.e., the lack of adequate local stress producing understimulation of the tendon cells), could lead to tensile weakening and degeneration over time [50,51]. For greater trochanteric pain syndrome, the role of compression seems to be clear: the gluteus medius and minimus tendons compress against the greater trochanter in positions of hip adduction [52]. Similarly, the deep fibers of the supraspinatus tendon are exposed to high compressive loads against the humeral insertion [53]. High levels of tendon compression and the associated tissue hypoxia stimulate the fibrocartilaginous metaplasia of tenocytes that differentiate into hypertrophic chondrocyte-like cells to produce calcium deposits (predominantly hydroxyapatite) [54,55]. The clinical sequela is a condition known as calcific tendinopathy [56]. The negative effects of the excess or lack of adequate local stress on the tendon can also be amplified by systemic factors such as metabolic alterations related to aging (i.e., obesity and type 2 diabetes) [57]. Therefore, age-related tendinopathies could be viewed as the result of a degenerative process underlain by local and systemic factors. However, neither the “failed healing model” nor the “degenerative model” of tendinopathy fully explains the heterogeneity of its presentation. The “continuum model” of tendon pathology was proposed in 2009 and revisited in 2016 by Cook et al. [58,59] to overcome the limitations of previous models. This model assumes that tendons may have discrete regions that are in different stages (normal, reactive, or degenerative) at one time. This model also assumes that regardless of the initiating event (overstimulation or understimulation of resident tenocytes, collagen disruption or micro-injury, or inflammation), tendon pathology is characterized by a significant cell response to injury. Therefore, a tendon cell-based response could occur in a structurally normal (to conventional imaging modalities at least) tendon portion that may drift in and out of a reactive response. Although the exact mechanisms responsible for tendon pain remain to be clarified [60], the “continuum model” also suggests that paracrine signaling by tenocytes could represent one of the drivers of nociception. In fact, cytokines released by tenocytes (and/or infiltrating immune cells) could sensitize peripheral mechanoreceptors near or in the paratenon (that could also be irritated by the increased tendon size) as well as nociceptor terminals, ultimately resulting in the stimulation of the peripheral nerve. However, mechanisms for tendon pain should extend beyond local tissue

changes and include increased axonal sprouting from repeated injury as well as peripheral and central mechanisms of nociception modulation [60].

3.4. Clinical Presentation

Core clinical characteristics of rotator cuff degenerative tendinopathy include old age, focal night pain, weakness of shoulder muscles, and movement restriction [61,62]. Shoulder pain generally radiates to the deltoid and the middle part of the upper arm. Weakness, movement restriction, or both, especially in active external rotation, are found in half of radiologically confirmed rotator cuff tears [62]. Movement testing helps to distinguish rotator cuff degenerative tendinopathy from frozen shoulder (adhesive capsulitis). Frozen shoulder is an idiopathic and self-limiting condition in which movement of the shoulder becomes restricted in both active and passive external rotation [63].

Calcific tendinopathy is another important, self-limiting differential diagnosis for patients presenting with shoulder pain, especially in middle-aged patients. It is a condition in which calcium deposits develop in the supraspinatus (80% of cases), infraspinatus (15% of cases), and subscapularis (5% of cases) tendons [55,56]. Calcific tendinopathy can be diagnosed through imaging of calcium deposits and may respond differently to treatments compared to degenerative tendinopathies [55,56].

Like shoulder tendinopathy, low-grade pain (with or without movement restriction) is characteristic of gluteal tendinopathy. This pain presents in the lateral hip and is aggravated with activities (such as walking and other weight-bearing activities) and side-lying on the affected side [52]. Further core clinical characteristics of gluteal tendinopathy include old age, female gender, comorbidities such as pain generated from the back and hip joint, overweight/obesity, poor abductor hip function, altered gait parameters, and psychological distress [3,4].

3.5. Management

The best approaches for clinical management of rotator cuff and gluteal tendinopathies have yet to be elucidated. Careful analysis of the medical history and symptoms must guide clinical decision making. Studied interventions include exercise, interventional approaches (i.e., corticosteroid or platelet-rich plasma injections), physical therapy modalities (radial pressure wave treatment and focused shock wave therapy), and topical glyceryl nitrate application.

Positioning and exercise therapy seem to be effective in both rotator cuff tendinopathy and greater trochanteric pain syndrome; however, it is unclear what protocol is the best. Overuse may be managed by reducing loads and improving biomechanics. Reducing compression must be evaluated carefully in static and dynamic positioning. In greater trochanteric pain syndrome, it is probably useful to advise patients to avoid hip-adducted positions, such as standing with “hanging on one hip” or standing with crossed legs. In the same way, patients with rotator cuff tendinopathy should avoid sustained work positions where the shoulder is unsupported in abduction. Exercises commonly start with isometric contractions because they are easy to perform, well-tolerated, and may have analgesic benefits [64]. Once pain is more tolerable, then a restorative exercise program with an early and gradually progressive tensile loading may improve the tendon’s architecture and function. Increased loading improves the load-bearing capacity, and low-velocity, high-tensile load exercises benefit the tendon structure [65]. Eccentric exercises provide additional strain that transmit higher forces through the joint [66]. As the symptoms continue to improve, more functional exercises, such as jumping, running, and throwing, can be added progressively. More detailed exercise programs for both shoulder tendinopathies and greater trochanteric pain syndrome can be found in the literature [67,68].

For both gluteal tendinopathy and degenerative rotator cuff tendinopathy, peritendinous corticosteroid injection provides moderate pain relief, but only for a short time (less than 4 weeks) [69,70]. Recent preliminary evidence suggests that platelet-rich plasma injections may also clinically benefit patients with gluteal tendinopathy [71–73].

However, a physiotherapy-led education and exercise program performs better than corticosteroid injection in the long-term follow-up of gluteal tendinopathy patients and should be considered

as first-line treatment [67]. Similar to the previous findings, Korakakis et al. [74] observed that corticosteroid injection is superior to radial pressure wave treatment in the short-term (1 month), but that physical therapy is superior to corticosteroid injection at mid-term (4 months) and long-term (>12 months) follow-up in gluteal tendinopathy patients. Moreover, focused shock wave therapy was effective in reducing lateral hip pain, both in the short-term (2 months) and mid-term (6 months) follow-up [75]. Given that the gluteal tendon insertion on the greater trochanter has variable depth to the skin surface, especially in female patients presenting a gynoid fat distribution [4,52], it is generally assumed that focused shock wave therapy is more effective compared with radial pressure wave treatment [76]. However, no previous study has compared these two modalities in the management of gluteal tendinopathy.

Regarding rotator cuff tendinopathy, there is consistent evidence that both focused shock wave therapy and radial pressure wave treatment reduce pain and improve shoulder function when degenerative tendinopathy is present [76,77]. Conversely, extracorporeal shock wave therapies may be less effective for calcific rotator cuff tendinopathy, while ultrasound-guided percutaneous irrigation treatment [55,78–80], also known as ultrasound-guided lavage [80], seems to be more effective than physical therapies or corticosteroid injection [80].

Experiments suggest that nitric oxide, a free radical produced by different enzymes, enhances new tissue synthesis through several processes. A randomized control trial showed significant improvement in tendinopathy-induced shoulder pain and function at 12 and 24 weeks with glyceryl trinitrate (1.25 mg/24 h) compared to placebo [81]. No studies are available about the effect of the glyceryl trinitrate in greater trochanteric pain syndrome.

4. Arthritis

4.1. Definition

Arthritis is a disease of articular joints that alters the joints biochemically, structurally, and physiologically. There are many classifications for arthritis since it is a heterogeneous, degenerative disorder with multiple etiologies and presentations [82]. Primary or idiopathic arthritis is without a specific or known antecedent and primarily affects the hands, hips, knees, and spine. Secondary arthritis has an underlying cause such as acute trauma or a rheumatologic, metabolic, or infectious disease. This historical categorization has continuously been challenged by our continued understanding of this widespread disease [83]. Therefore, multiple descriptive categories have been proposed for joint size, local or generalized joint involvement, and clinical, biochemical, and radiological presentations [82]. In practice, the terms “arthritis” and “osteoarthritis” most commonly refer to the primary, degenerative “wear and tear” of chronic joint use and exclude autoimmune subtypes (e.g., psoriatic arthritis, rheumatoid arthritis, and spondyloarthritis) and acute secondary causes (e.g., gout and infection). This has remained the practical definition even though we continue to find overlaps in pathological processes [84,85].

4.2. Epidemiology

Osteoarthritis is a leading cause of pain and disability around the world [86]. Utilizing the 2010 Global Burden of Disease study, the WHO states that 10% of men and 20% of women over the age of 60 have symptomatic osteoarthritis [87]. The Johnston arthritis study found the lifetime risk of symptomatic knee osteoarthritis to be “nearly 1 in 2 overall” and “more than 2 in 3” for obese people [88]. Based on the United Nations’ population predictions, the WHO suspects that 130 million people will have symptomatic osteoarthritis by 2050 [89].

4.3. Pathophysiology

The main reason cited for the increasing prevalence and disability of osteoarthritis is our aging population. Biochemical and mechanical changes associated with aging are the greatest non-modifiable

risk factors for osteoarthritis development and progression [90]. Women have a higher prevalence and severity of osteoarthritis, especially in the hands, hips, and knees. However, results suggesting that estrogen plays a role in incidence and progression have been conflicting [91]. Joint-specific variations are seen in different ethnic and racial groups, but osteoarthritis exists across all populations [92]. Multiple osteoarthritis genetic loci on genome-wide scans have been identified that may help to elucidate the pathophysiology and associated phenotypes in the future [93].

Osteoarthritis starts as a biochemical process affecting the synovium, cartilage, or subchondral bone and progresses to biochemical and anatomical abnormalities of the entire joint complex, culminating in illness [82,89,92]. The initial phases of this biochemical process consist of joint inflammation, as documented by Driban et al. through synovial fluid protein concentration analyses [94]. The joint inflammation could be initiated by mechanical trauma, metabolic changes, aging, or a combination of these factors. Obesity is thought to induce a local, mechanical trauma, especially on the knees. One unit of weight loss leads to a 4-unit reduction in knee load per step [95]. Obesity also contributes to osteoarthritis in non-weight-bearing joints of the hand, supporting the pathophysiological contribution of systemic metabolic inflammation to osteoarthritis incidence and progression [96]. Likewise, alcohol and nicotine both contribute to systemic inflammation and could potentiate pro-inflammatory mediators in the joint complex. Trauma, whether related to a major joint injury or occupational microtrauma, destabilizes and deforms the joint, worsening the mechanical forces affecting the cartilage and subchondral bone. Ligament laxity, sarcopenia (especially related to quadriceps weakness in knee osteoarthritis), and osteoporosis also contribute to the progression of osteoarthritis [1,2,92].

The synovium can be the source of multiple pro-inflammatory mediators that lead to pain and changes to the synovial fluid. The synovial fluid nourishes the avascular, aneural cartilage as well as produces hyaluronic acid (HA) and lubricin to reduce friction during movement. An increase in pro-inflammatory and catabolic products decrease the concentrations of cartilage-protecting factors and increase the production of cartilage degradation factors. There are also changes to the molecular weight of HA and a decrease in the concentration of lubricin [97].

The cartilage is also protected from mechanical stress and nourished by the subchondral bone. Early osteoarthritis bone remodeling could occur through different mechanisms: cellular signaling leading to bone remodeling and resorption and vascular invasion leading to cartilage degeneration and diminished mechanical integrity. As osteoarthritis progresses, there is a net increase in remodeled bone formation, leading to the characteristic osteophytes, sclerosis, and joint deformity seen in advanced disease [89,92].

When an imbalance exists in the structure or functioning of the extracellular matrix of the cartilage, additional inflammatory mediators and mechanical stress create a “vicious cycle” of cartilage degeneration. Over time this “low-grade” inflammation and mechanical stress limit chondrocyte production of functional collagen (collagen type I), reduce space-occupying proteoglycans, and increase inflammatory mediators. While mechanical stress can occur over time and increase with age, there is likely an inherent age-associated change in the chondrocyte phenotype that also impairs cartilage homeostasis [89,92]. This change leads to multiple molecular events and consequences (including altered gene expression related to senescence, DNA and telomere dysfunction, altered protein secretion, oxidative damage, decreased growth factor response, and apoptosis), precipitating cartilage destruction and susceptibility for osteoarthritis in the elderly [90,98].

4.4. Clinical Presentation

Patients with osteoarthritis can be identified through a range of common phenotypes, the presence of risk factors, clinical signs, and symptoms [99].

Patients presenting with osteoarthritis complain of short-lived (<30 min) pain and joint stiffness at the beginning of movement, especially in the morning. As osteoarthritis worsens, pain can be present after a period of activity or become continuous. Pain and stiffness create a functional limitation in movement, affecting the ability to perform activities of daily living. Primary physical exam

findings can include crepitus, restricted movement, and bony enlargement (Heberden, Bouchard, and Luschka's joint). There is no or only minimal palpable warmth, redness, or effusion in joints affected by osteoarthritis. Through the progressive increase in pain and loss of mobility, reduction in fitness and social isolation can be common [89,92]. Consistently, previous studies suggested that chronic pain and reduced fitness, common in patients with osteoarthritis, contribute to depression, obesity, cardiovascular disease, and decreased quality of life—potentiating the risk of overall morbidity and mortality [89,92].

Radiography is considered as the “gold standard” for osteoarthritis diagnosis and is commonly used to identify the severity and to monitor the progression of joint disease in symptomatic patients [89,92]. Kellgren and Lawrence [100] proposed a prominent system to classify radiographic osteoarthritis changes and look for osteophytes, joint space narrowing, subchondral sclerosis, and deformity. The absence of radiological evidence of osteoarthritis does not eliminate the possibility of disease, and the presence of radiological evidence does not directly correlate to patient symptoms. Therefore, nearly all leading osteoarthritis groups state that an appropriate diagnosis can be made on clinical presentation alone in a symptomatic elderly adult [89,92,101], though radiographs likely add diagnostic specificity [102]. Additional imaging (e.g., magnetic resonance) and laboratory findings (e.g., synovial fluid and serum analyses) rule out other causes of joint pain, assist in research advances, or prepare for surgical intervention. Furthermore, the abovementioned clinical variables, alone or in combination with radiological variables, can also be useful for patient stratification [103]. For example, a stratification based on the severity of symptoms distinguishes between asymptomatic and symptomatic arthritis sufferers, while a stratification based on imaging findings distinguishes between diffuse disorder and joint-specific disorder. Driban et al. [104] have provided recent evidence that age, glucose concentrations, body mass index, and static alignment are the most important variables for classifying individuals with incident accelerated knee arthritis. Stratification techniques based on clinical and radiological variables may be the key to developing disease-modifying interventions for subsets of patients within this heterogeneous disease [103].

4.5. Management

Multiple protocols for therapeutic management of osteoarthritis exist, including those from the European League Against Rheumatism (EULAR) [101], European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [105,106], Osteoarthritis Research Society International (OARSI) [107], and American College of Rheumatology (ACR) [108,109]. Treatment algorithms from these organizations and others can roughly be broken into three, stepwise segments: (1) lifestyle treatments, (2) pharmacologic treatments, and (3) interventional treatments.

First, all osteoarthritis organizations support patient information and education about their condition to promote mechanical and metabolic improvements. These include self-management, weight loss, and an exercise program to strengthen the joint and supporting structures. Additionally, a psychosocial assessment is likely beneficial for patients with chronic pain. Weight loss and obesity treatment is a universal recommendation, though many recognize the difficulty of achieving success [92]. ESCEO's comprehensive recommendations in 2014 highlighted the need for weight loss and included an endorsement of 5% weight reduction in 6 months with the goal of 10% weight loss to achieve significant symptom benefit [105]; however, ESCEO's 2019 update admitted to a lack of evidence-based treatment regarding weight management and physical exercise [106]. Exercise programs vary in their specific recommendations and generally encourage both cardiovascular and strength training (specifically quadriceps strengthening) [110]. Physical therapy and supervised, progressive exercise programs are encouraged, especially if they successfully transition into a self-administered home program [111]. Aquatic exercises are useful, especially if land-based activities are too painful [108]. A walking cane can help with functional movement when pain is present [106,108]. Braces, splints, and taping can be used for comfort or to provide mechanical support of a deformity depending on the location of the offending joint [110]. Recommendations for wedged insoles are mixed, but generally

negative due to limited improvement and possible side effects [110]. Guidelines are also mixed regarding the most common physical therapy modalities, including thermal (heat/cold) application, manual therapy, acupuncture, and electrotherapies [112].

Pharmacologic treatment recommendations vary depending on the joints affected and patient comorbidities. The most common initial treatment recommendation is acetaminophen (paracetamol) due to its favorable side-effect profile [110]. ESCEO diverges from this recommendation (due to paracetamol's minimal benefit and possible side effects) and recommends the use of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) with prescription grade-only crystalline glucosamine sulfate or chondroitin sulfate as a first-line pharmacologic treatment of symptomatic osteoarthritis [106]. This was not supported by neither the 2012 nor the updated 2019 ACR recommendations [108,109], but it should be noted that prescription-grade SYSADOAs are not available in the United States. Capsaicin is a topical agent with mixed support that could be used if tolerated [107]. If the patient is still symptomatic, NSAIDs are considered by all osteoarthritis treatment algorithms [110]. Due to bleeding, renal, and cardiovascular risks, topical NSAIDs should be considered first for superficially located joints [106,107,110]. COX-2 inhibitors with a proton-pump inhibitor should be considered in the setting of gastrointestinal risk. However, COX-2 inhibitors should be avoided in patients with known cardiovascular risks. Patients with glomerular filtration rate < 30 cc/min should avoid all NSAIDs [106]. Opioids, especially tramadol, are recommended for severe pain, but should be used with caution due to concerns of addiction, abuse, and diversion [106–109]. OARSI, ESCEO, and ACR additionally support duloxetine for patients with multiple symptomatic joints and signs of central sensitization [106–109].

Interventions for osteoarthritis typically begin with intraarticular injections and can escalate to total joint replacement. Corticosteroid injections can temporarily help with pain (<3 weeks) and are generally recommended when there are additional signs of inflammation like breakthrough pain or a mild effusion, but not on a continuous basis [106,107,109,110]. Intra-articular hyaluronate (viscosupplementation) can also improve pain and joint inflammation and is a popular alternative to steroids. Formal recommendations, however, remain controversial due to mixed research results, cost, and availability; the most recent guidelines (by ESCEO and ACR) offer no to low-strength recommendations for its use in the hip and knee [106,109,110]. With our aging population, total joint replacements are becoming more prevalent [113]. Surgical intervention remains reserved for patients with daily pain despite conservative treatment to ensure the benefits outweigh the risks [89,92].

5. Conclusions

We reviewed the literature relative to three inter-related musculoskeletal disorders (i.e., sarcopenia, tendinopathies, and arthritis) that are highly prevalent in elderly subjects, in order to highlight the pathophysiological common denominator and propose strategies for personalized clinical management of patients presenting with this combination of disorders. Even though their clinical presentation can be different (loss of skeletal muscle mass and function in sarcopenia, persistent tendon pain and loss of function in tendinopathies, and persistent joint pain and stiffness in arthritis) [7,36,89,92], the three disorders have common pathophysiological and clinical characteristics. On the basis of the general content of this article, we report in the following a non-comprehensive list of highlights relative to the common pathophysiological and clinical characteristics of the three disorders.

1. The progressive loss of (focal or generalized) neuromuscular performance is the pathophysiological denominator common to the three disorders [7,13,22,24].
2. The three disorders increase the risk of adverse outcomes such as pain, motor impairment, increased risk of falls and fractures, impaired ability or disability to perform activities of daily living, and reduced quality of life [13,59,89,92].
3. The three disorders have a heterogeneous clinical presentation: patient stratification based on clinical and imaging variables may be the key to developing disease-modifying interventions for different subsets of patients [103,104].

4. The precise management of the three disorders requires not only the use of available tools and recently proposed operational definitions, but also the development of new tools and approaches for prediction, diagnosis, monitoring, and prognosis of the three disorders and their combination.
5. Physical exercise, alone or in combination with nutritional interventions, is the approach currently recommended as the primary treatment of the three disorders [24,25,49,67,107].

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Review

Central and Peripheral Neuromuscular Adaptations to Ageing

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Abstract: Ageing is accompanied by a severe muscle function decline presumably caused by structural and functional adaptations at the central and peripheral level. Although researchers have reported an extensive analysis of the alterations involving muscle intrinsic properties, only a limited number of studies have recognised the importance of the central nervous system, and its reorganisation, on neuromuscular decline. Neural changes, such as degeneration of the human cortex and function of spinal circuitry, as well as the remodelling of the neuromuscular junction and motor units, appear to play a fundamental role in muscle quality decay and culminate with considerable impairments in voluntary activation and motor performance. Modern diagnostic techniques have provided indisputable evidence of a structural and morphological rearrangement of the central nervous system during ageing. Nevertheless, there is no clear insight on how such structural reorganisation contributes to the age-related functional decline and whether it is a result of a neural malfunction or serves as a compensatory mechanism to preserve motor control and performance in the elderly population. Combining leading-edge techniques such as high-density surface electromyography (EMG) and improved diagnostic procedures such as functional magnetic resonance imaging (fMRI) or high-resolution electroencephalography (EEG) could be essential to address the unresolved controversies and achieve an extensive understanding of the relationship between neural adaptations and muscle decline.

Keywords: aging; cerebral cortex; dynapenia; elderly; motor unit; muscle strength; neural; neuroplasticity; sarcopenia

1. Introduction

Ageing is associated with loss in muscle mass and strength. Originally, scientists conceptualised the term “sarcopenia” to describe the age-related loss of skeletal muscle mass [1,2]. Others coined the term “dynapenia” to indicate the decline in muscle strength [3–6]. More recently, numerous investigators introduced the term “muscle quality” to describe the relationship between muscle strength and size in older adults [7–10]. However, whereas the large majority of the research has focused on the intrinsic skeletal muscle properties and mechanisms to explain muscle weakness in older adults, relatively little recognition has been given to the potential role of the central nervous system as a fundamental component of the decline in muscle function [11].

Researchers have suggested that the age-related decay in muscle quality can be attributed to many neural factors, including a decline in the function of the human cortex, spinal cord and neuromuscular junction [12]. Investigating the role of neural factors in preserving muscle properties and contraction capacities is key to developing a more comprehensive understanding of the causes leading to the decline in muscle function occurring at advancing age. In this review, we highlight the neurological and neuromuscular adaptations that primarily cause impairments in the skeletal muscle function and performance of the aged population.

2. Supraspinal Age-Related Adaptations

Premotor and primary motor cortical areas comprise a large number of excitatory and inhibitory neurons, including glutamatergic neurons, axonal projections and pyramidal neurons [13]. Besides projecting to the cortical areas of the central nervous system, these neurons form a long axonal connection with the lower motor neurons in the ventral horn of the spinal cord [13]. Several studies have shown that the premotor and the primary motor cortex (M1) incur cortical atrophy [14–17]. The total volume of the cortical area has been shown to decrease (between 4% and 16%) with age [14–16]. In the past, it was commonly assumed that this was attributed to a decrease in the number of M1 neurons during ageing. However, recent evidence suggested that, rather than a numerical decay in cortical neurons, M1 cortex decline is related to a volumetric reduction in premotor and primary motor neuron cell body size and synaptic density [16–18]. This adaptation has been referred to as neural atrophy [19]. A study on cadaveric dissections [20] demonstrated that the elderly population had an average of 43% volumetric reduction in the motor cortex cell body size compared to young adults. These findings have been more recently supported by studies performed on living humans using high-resolution magnetic resonance. Salat et al. [17] found that the cerebral cortex, including M1 cortex, incurs a substantial reduction in volume due to the morphometric changes in the neural cells. Several studies evidenced a strong correlation between cortical atrophy and fine movements, such as mirror drawing [21]. Other motor tasks appear to be substantially influenced by grey matter atrophy. Rosano et al. [22] reported a decline in gait performance during GaitMat walking proportional to the decrease in grey matter volume. Similarly, Sridharan et al. [23] illustrated a strong correlation between lower grey matter volumes and impaired reaching movements in aged rhesus monkeys.

Neural atrophy, however, is not the only morphometric adaptation that occurs during ageing. A major alteration involves the cortical white matter, which exhibits a significant decrease in subjects over 65 years old [24,25]. White matter is predominantly made up of glial cells and myelinated axons, and it is responsible for the cortico-cortical and cortico-spinal connectivity. Cross-sectional studies indicate a profound disruption in the integrity of the white matter [25], which declines with age at an average rate of 2.5% every ten years [26,27]. The experimental investigation of Marnier et al. [28] indicated that myelinated nerve fibre length in the white matter significantly decreased in aged population compared to younger individuals. Age-related morphometric adaptations of the motor cortex may therefore carry a considerable effect on the connectivity within the cortical areas as well as between the cortex and the rest of the central nervous system [29]. Several studies have indicated that a decrease in white matter integrity is associated with slower motor performances on interhemispheric transfer task such as alternating finger tapping [30] and other fine finger movement tasks [31]. Zahr et al. [32] demonstrated that greater white matter integrity correlates with improved motor performance for both fine and gross motor skills. Other researchers indicated that white matter hyperintensities lead to poorer stability, expressed as greater sway path and impaired static balance [33].

Age-related decline in motor functions has also been imputed to impaired neurotransmission, which is regulated by neurochemical factors. Evidence suggests that alterations in neurotransmitters (NT) and their specific receptors are directly associated with impairments of the cognitive and motor function in the elderly population. Abnormalities in the NT-regulated systems such as serotonergic [34,35], cholinergic [36], adrenergic [35], dopaminergic, GABAergic and glutamatergic [37–40] have been highlighted in ageing individuals. Although a comprehensive understanding of how each system

responds to ageing remains unclear, several investigators suggested that the interaction between glutamate, dopamine and GABA plays a critical role in the decline of cortical and motor functions in the elderly [40]. The NT-regulated systems' alterations have been associated with increased neural noise, which has been defined as a random background activity in the brain signal [11].

Failures of the glutamatergic system have been ascribed as one of the neurochemical mechanisms responsible for the increase in neural noise since glutamate is directly involved in the modulation of the excitatory inputs in the central nervous system. The study of Arnth-Jensen et al. [41] demonstrated that ageing is accompanied by a significant reduction in the glutamate uptake. They found an excessive quantity of extracellular glutamate around cortical neurons and observed a significant increase in neural noise which is expressed by abnormal and unpredictable neural background activity even during simple motor tasks.

Furthermore, evidence exists that increased neural noise can be attributed to a decline of the dopaminergic system [42]. A previous investigation evidenced a considerable loss of dopamine transporters in the central nervous system with a 6.6% decay per decade in healthy individuals [43]. MacDonald et al. [44] used position emission tomography (PET) and found that increased reaction times in the aged population is closely related to the loss of dopamine receptors. Using imaging techniques like PET, researchers have reported a strong correlation between level of striatal dopamine transmission and motor decline in balance and gait parameters [45,46]. Moreover, the dopaminergic system has proven to be associated also with fine motor control, especially in older adults [47,48]. It has been suggested that failure of the dopaminergic system in aging might underlie the reduced velocity and control of fine movements [48]. Other researchers suggested that the alterations of the dopaminergic system can be due to the reduced inhibitory modulation which is regulated by the GABA neurons [40]. Inhibition of dopamine release and glutamate uptake occurring could potentially affect the ability to produce force and to preserve motor control in the elderly [11].

The GABAergic inhibitory system also plays an important role in isolating movements and retain brain neuroplasticity. A few investigators have suggested that neuroplasticity can be preserved almost entirely in the ageing brain [49–52]. Nevertheless, many researchers have reported that brain neuroplastic and neuromodulatory capabilities substantially decrease in the elderly population [53–55]. The GABAergic inhibitory system has been generally analysed in research using transcranial magnetic stimulation (TMS) [56,57], which has been proven to be a reliable method to assess neural inhibition and cortical excitability. Many TMS studies evidenced that the elderly population is characterised by a severely impaired sensorimotor integration of afferent input [54–56,58]. Fujiyama et al. [55] showed that a reduced capacity of GABA-mediated inhibition has a clear impact on short-interval intracortical inhibition during response preparation for a motor exercise. These findings were more recently supported by those of other authors [59–64]. Nonetheless, the effect of ageing on the GABAergic system has raised many questions and many discrepancies have emerged in the literature as recently described in a comprehensive review [65].

As previously stated, several TMS studies reported that ageing is associated with a decline in intracortical inhibition. Conversely, three studies reported an increased inhibition in older adults [66–68]. Furthermore, other researchers found very little to no effect of ageing on intracortical inhibition [54,69–71]. These inconsistencies between studies may be related to methodological differences, such as different TMS protocols, as well as differences between resting-state and task-related TMS assessments. To improve the interpretation of the cortical inhibitory-excitatory circuits, the TMS technique has been recently combined with electroencephalography (EEG) as in the study of Opie et al. [68] or brain imaging techniques such as magnetic resonance spectrometry (MRS) [65] and functional magnetic resonance imaging (fMRI), although the latter is limited by the inability to distinguish between inhibition and excitation [72].

Although GABAergic system failures can represent a valid and plausible reason to the age-related loss in cortical plasticity and corticospinal excitability, other factors, such as a decline in long-term potentiation [59] or altered gene expression [73], must be considered and further analysed.

3. Spinal Age-Related Adaptation

Advanced age is accompanied by a spinal neurodegenerative process, which includes both a structural and functional reorganisation at the spinal level. The most critical morphological alteration occurring in the spinal region is represented by spinal atrophy. This is primarily related to the loss of spinal motor neurons due to the apoptosis of the neural cells. In addition, the loss of motor neurons appears to be associated with an increase in the number of astrocytes as well as an alteration of the dendritic networks [74]. Several human studies also reported a reduction in the density and diameter of myelinated and unmyelinated axons in the ventral horns of the spinal cord of aged individuals [75–80]. Jacobs and Love [81] demonstrated that old adults show a decline in myelinated and unmyelinated fibres of 38% compared to young adults. Similarly, a study performed on aged rodents revealed that ageing is characterised by a loss of around 40% in the myelinated and unmyelinated fibres compared to young individuals [82]. Consistently, these authors reported a reduced axonal density and myelin thickness along with a considerable infiltration of connective tissue and increase of infolded and outfolded myelin loops [81–83].

One of the reasons for the age-related neurodegeneration at the spinal level has been attributed to a reduction of the endocrine and paracrine production of insulin-like growth factor-1 (IGF-1). IGF-1 provides not only an effective prevention mechanism, but also a compensation mechanism for the loss of spinal motor neurons with advancing age. Investigators have shown that IGF-1 plays an important role in motor neuron apoptosis, motor axon myelination, stimulation of axonal sprouting and repair of axons [84]. Although the mechanism underpinning the reduction of IGF-1 is still poorly understood, it appears that the inflammatory response which characterised the majority of elderly individuals may affect the local production of IGF-1. Grounds [85] observed an elevated level of inflammatory cytokines TNF- α and TNF- β in older adults and reported a strong correlation between the inflammatory response and the impaired IGF-1-mediated effects on motor neuron regeneration and axonal repair. The importance of IGF-1 on facilitating axonal sprouting has been demonstrated in animal experiments. In a study on young mice, a higher concentration of IGF-1 was accompanied by a greater capacity to reinnervate denervated muscle fibres after motor neurons loss [86]. The authors claimed that reinnervation through axonal sprouting can compensate for the loss of almost 50% of the original motor neurons.

Disfunction of spinal motor neurons, as well as reduced axonal myelination and reduced internodal length, have been considered responsible, at least in part, for the age-related decrease in nerve conduction velocity. Reductions in peripheral efferent and afferent axon action potential conduction velocity have been often reported in the literature [82,87–91]. Rivner et al. [92] demonstrated that advancing age highly correlates with variations of nerve conduction velocity and both motor and sensory responses. The analysis of the Hoffman (H) reflex via electromyography (EMG) and nerve stimulation has been proven to be a valid method to assess the efficacy of spinal circuitry function [93]. H-reflex primarily indicates the efficacy of Ia sensory afferent fibres to activate spinal motor neurons. Furthermore, EMG and nerve stimulation allow the analysis of the motor (M) wave which measures the direct activation of peripheral motor axons and, therefore, the magnitude of the motor response.

Many investigators revealed a significant reduction in the amplitude of the H-reflex response in old compared to young individuals. [94–99] This suggests that ageing may determine a decline in spinal motor neurons excitability although other factors such as pre-synaptic inhibition must be taken in consideration [100]. Along with a reduced H-reflex amplitude, the authors demonstrated that ageing is associated with an increased H-reflex latency [89,98]. These findings may help interpret the decline in peripheral nerve conduction velocity occurring at an advanced age. Interestingly, the research of Scaglioni et al. [89] revealed that M-wave latency was not different between young and aged individuals, in contrast to what emerged for the H-reflex latency. The same authors suggested that ageing could, therefore, affect sensory afferent fibres to a greater extent compared to efferent motor axons [89].

Another mechanism that seems to contribute to the spinal circuitry failures in aged individuals is the impaired modulation of the pre- and post-synaptic spinal inhibition [101]. Some investigators indicated that healthy young adults increase their muscle force by down-regulating their pre-synaptic inhibition, which, in turn, leads to enhanced excitatory afferent input. The research of Earles and co-workers [96] demonstrated that during an isometric voluntary contraction of a leg muscle, older participants exhibited a reduced modulation of spinal pre-synaptic inhibition although they were able to modulate the force similarly to young participants. Similarly, the work of Baudry et al. [102] indicated that older individuals did not modulate the amount of pre-synaptic inhibition of Ia afferents during a wrist extension task but rather increased the coactivation of the antagonist muscle. This appears to be related to a deterioration of the spinal afferent input and suggests that the elderly tend to rely less on spinal mechanisms and more on supraspinal mechanism in order to increase force [103].

4. Neuromuscular Junction

The progressive neuromuscular decline during ageing, as previously stated, can be accompanied by failures of the de-innervation–re-innervation mechanism, which normally compensates for neuronal loss and the related impairment in muscle strength and control. It appears that age-related neuromuscular junction (NMJ) dysfunction can primarily explain the progressive decline of the re-innervation process. As the majority of the human structures, also NMJ occurs in morphological remodelling and functional impairment as individuals age. Structural changes generally occur in the pre-synaptic area (motor nerve terminal) and post-synaptic area (muscle fibre surface and membrane), where the number of post-junctional folds in the motor endplate is significantly reduced, resulting in slower conduction velocity and decreased magnitude of the muscle action potentials [104,105]. Alterations of the nerve terminal region primarily include a numerical reduction of mitochondria in the plaque of the motor neuron terminal bouton. Mitochondria play a fundamental role in regulating metabolism, signal transduction and cell apoptosis and produce oxygen free radicals [106]. In addition, axonal mitochondria also function as a buffer for the calcium ion loads essential for excitation–contraction coupling [107].

Investigators have reported several morphological adaptations of the axonal mitochondria. Garcia et al. [108] indicated that mitochondria in the NMJ of the ageing population may incur cristae disruption, swelling and multiple fusions [109]. Studies regarding the pre-synaptic plaque have shown high levels of oxidative damage and nitrosylation. This appears to be directly responsible for the deterioration of the pre-synaptic mitochondria [110]. Some authors suggested that in the motor nerve terminals and the post-synaptic endplate, which are highly metabolically active, mitochondrial dysfunction may induce an even greater impairment [111,112]. In addition, Ibejunjo et al. [113] have recently indicated the presence of downregulation of mitochondrial energy metabolism in rats with NMJ disruption. However, the impact of oxidative stress on age-related adaptations of the peripheral nervous system remains still unclear and requires further investigation [108,114].

An author reported that in aged mitochondria located in the NMJ, there is evidence of altered calcium buffering and reduced ATP production, which may negatively affect both neurotransmission and vesicular recycling [115]. This suggests that the impaired excitation–contraction coupling occurring in elderly individuals could be closely related to the dysfunction of axonal mitochondria. However, some investigators have argued that the neurotransmission dysfunction is mainly associated with the age-related reorganisation of neurotransmitters receptors such as nicotine acetylcholine receptors (nAChR), which are found in the post-synaptic membrane, dihydropyridine receptors (DHPRs), which are located in the sarcolemma, and ryanodine receptors (RyRs) of the sarcoplasmic reticulum [116]. In particular, excitation–contraction uncoupling appears to be related to the mismatch between DHPRs and RyRs found in aged individuals. The interaction between DHPRs and RYRs plays a crucial role in the regulation of the calcium ions during contraction stimuli. Severe dysfunctions of these two receptors lead, in turn, to a decreased calcium release after an action potential, thus an impaired contraction [117,118].

Delbono [119] indicated that IGF-1 has a role in preventing the age-related failure of neurotransmitters receptors. A recent animal study suggested that overexpression of IGF-1 in mice can significantly reverse the numerical decrease of DHP receptors, thus preventing the dysfunction of the post-synaptic NMJ [120]. As previously described at the spinal level, there is strong evidence that IGF-1 can improve nerve regeneration and prevent neuronal loss. Moreover, many authors have highlighted the importance of IGF-1 in maintaining the integrity of the NMJ [121] and promote the re-innervation of previously de-innervated motor units in aged individuals [122].

The age-related structural and functional adaptations occurring at the NMJ have been further associated with other neuromuscular alterations such as reduced number of synaptic vesicles [123], reduced amounts of released neurotransmitters [115], a decline in satellite cell proliferation [124] and fragmentation of Schwann cells [125,126]. Several recent studies on Schwann cells emphasised their critical importance in neurodegenerative prevention, particularly concerning the NMJ synapse. In light of their capacity to regulate axonal regeneration, assist neural re-myelination fibres and provide functional recovery, degeneration of these cells might strongly contribute to ineffective re-innervation and neuromuscular dysfunction in ageing [127–129].

Authors have suggested that many NMJ impairments can be related to the high level of circulating inflammatory markers, such as cytokines and interleukines, which are commonly found in aged individuals. Elderly people generally incur chronic low-grade inflammation, also referred to as “inflammaging” [130], which represent a considerable risk factor for an accelerated decline of the neuromuscular structures, including NMJ. Previous literature clearly indicated that individuals suffering from chronic inflammation show evidence of muscle wasting and weakness [131,132]. In the NMJ, two mechanisms have been mainly identified in association with ageing inflammation. In the work of Saheb-Al Zamani et al. [133], overexpression of the interleukine 6 (IL-6) was found closely correlated with degeneration of Schwann cells in elderly, underlining the negative effect of inflammation on axonal regeneration. Furthermore, as reported in the previous paragraph, high levels of cytokines (TNF- α and TNF- β) in the aged population appear to down-regulate the production of IGF-1 and impair its regeneration activity [84].

Although there is indisputable evidence that elderly people present signs of muscle denervation and NMJ dysfunction, there is still no clear agreement if this process anticipates muscle sarcopenia or is a result of the decline of muscle fibres. Unfortunately, direct studies of the NMJ in humans are extremely challenging due to the delicate accessibility of its structures. The animal studies reported in this review have always required invasive surgical interventions (such as muscle needle biopsies) which are not commonly performed for research purposes in humans.

In living humans, insight into the NMJ decline during ageing is mostly reported via EMG assessments of single motor unit action potentials [134]. Current works on ageing NMJ have revealed severe alterations in the EMG recordings of single motor units. These consisted of abnormally large intervals between action potentials of two fibres of the same motor unit (Jitter) and higher variability in the shape of a single motor unit during consecutive discharges (Jiggle) [135,136]. Developing new neurophysiological techniques could be key to fully understanding the mechanisms underpinning the age-related neurodegeneration of the human NMJ. Substantial signs of progress have been made in the understanding of the molecular basis behind NMJ dysfunction through the analysis of circulating biomarkers as addressed in this paragraph. This area of investigation has a strong translational potential although the role of biomarkers, and their correlation with ageing neurodegeneration is not fully understood.

5. Muscle Fibre

Motor unit remodelling characterises elderly individuals and results in a considerable loss of innervated muscle fibres and a decrease in active fibres size [136,137]. Rates of fibres denervation greatly overcome re-innervation, and the decline in fibre size is closely related to the increase of

oxidative stress and cell apoptosis, with significant reductions in the number of satellite cell responsible for muscle fibres regeneration [138,139].

Old humans generally exhibit muscle atrophy, which consists of smaller fibres in the active motor units compared to young adults. [140–142]. Reduced fibre cross-sectional area appears to occur across all fibres, although studies have reported contrasting results with significant variability determined by muscle type and sex of participants [137,143]. Age-related atrophy has been often associated with decreased protein synthesis and fewer satellite cells particularly in type II fibres [144–146]. In addition, histochemical studies in both humans and animals showed that older individuals tend to exhibit multiple myosin heavy chain (MHC) isoforms in single fibres [147]. The expression of multiple MHC isoform in older adults could often impede the conventional categorisation of muscle fibres in type I and type II.

Some studies indicated that muscle-specific tension may be retained with ageing despite the decrease in muscle fibre size [142,148]. Nonetheless, several works on old and very old individuals reported lower specific tension across different muscles at advancing age, especially in participants of 80 years or more [149,150]. The authors suggested that lower specific tension could be related to a decreased level of intracellular calcium and calcium sensitivity which characterise older individuals [151,152]. Animal studies have shown reductions of specific tension associated with excitation coupling impairments as comprehensively reviewed by Delbono [153]. The discrepancies in the findings on specific tension of single fibres in aged muscles seem to be related to sampling bias due to neglect of lifestyle modifiers such as physical activity and nutrition. Physical activity appears to strongly influence specific tension [150], thus studies with participants matched for physical activity are required to better understand the extent of specific tension decline at advancing age.

In old individuals, contractile properties of the muscle fibres equally decline as age increases [141]. In particular, old adults show reduced contractile speed compared with young people with several studies reporting lower rates of force development [154] and decreased maximal shortening velocity in single muscle fibres [149,155]. This decline has normally been associated with an impairment of the cross-bridge kinetics [143]. Authors have suggested that any age-related shift from type II to type I fibres can induce a compelling reduction in peak power and contractile speed up to six times lower compared to young adults [148].

Similar to contractile speed, also the rate of muscle relaxation appears to be reduced with ageing [156–158]. Authors indicated that alterations of the cross-bridge mechanics as well as reduced calcium uptake and calcium-ATPase activity are primarily responsible for impaired muscle relaxation in older people [159].

6. Conclusions and Perspectives

In this review, we analysed the most updated literature regarding central and peripheral adaptation occurring during the ageing process. The increased aged population has required and requires a more comprehensive understanding of the mechanisms involved in muscular decline due to its strong correlation with disability and mortality. When possible, we have highlighted the studies in which physiological changes were associated with functional outcomes.

The emerging picture is that ageing determines a structural and functional reorganisation at the central and peripheral level which, in turn, causes impairments in voluntary activation capacity and reduction in motor performance. Although studies have reported large variability in voluntary activation within older adults, there is evidence that elderly individuals show impairments in voluntary activation which varies in magnitude depending on the task performed and the muscle groups involved [160–162].

Neural factors, such as cortical adaptations appear to play a fundamental role in the deterioration of muscle quality, although a strong theoretical rationale often has not been accompanied by equally valuable evidence. Whilst the majority of scientists widely agrees on the structural remodelling of the ageing brain and the resulting motor impairments, further research is required to fully understand

whether age-related reorganisation of inhibitory and excitatory circuits derive from neural malfunction or serve as a compensatory mechanism to preserve motor control in older individuals. Unanswered questions and literature inconsistencies may be addressed by combining newly developed diagnostics techniques and optimised procedures such as TMS in combination with novel brain imaging techniques (fMRI, MRS, magnetoencephalography) and electrophysiological monitoring techniques as, for instance, high-resolution EEG [163].

Age-related impairments occurring at the spinal level and in the NMJ area have been extensively analysed in the past and more recent research, but yet, a lack of agreement has arisen between different investigators. Introducing novel neurophysiological techniques as well as improving the understanding of the relationship between neuromuscular mechanisms such as pre- and post-synaptic inhibition and muscular voluntary activation could help resolve the discrepancies emerged in the literature. As previously described, the analysis of circulating biomarkers has carried a notable insight on the molecular basis behind the neurodegenerative process involving the spinal circuitry function and the NMJ. Further research is required to fully understand this process and the related mechanisms, in consideration of the strong translational potential of this area of research.

In order to understand the neuromuscular adaptations occurring at advancing age, several researchers have suggested the need to analyse the changes in neural drive to the muscles [164]. Surface EMG can provide some information on the neural drive to the muscles although the conventional procedures have been long debated and led to controversial conclusions, mainly due to the unavailability of motor unit population data. Recently, a novel, high-density EMG technique has been introduced to improve the estimation of the neural drive to the muscles [165]. Through the use of an array of electrodes rather than the usual bipolar configuration, a more accurate decomposition of the EMG signal appears to be feasible and it has shown promising results with regards to neural drive and motor unit properties estimation. Only few studies that used high-density EMG have been performed on elderly adults [166,167]. They reported evidence of impaired motor unit discharge characteristics which indicates a reduced integrity of the motor unit firing modulation [165,166]. Developing this technique could be key to more extensively interpreting the neural and intrinsic changes occurring with ageing.

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Review

Biohumoral Indicators Influenced by Physical Activity in the Elderly

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Abstract: In the scientific landscape, there is a growing interest in defining the role of several biomolecules and humoral indicators of the aging process and in the modifications of these biomarkers induced by physical activity and exercise. The main aim of the present narrative review is to collect the available evidence on the biohumoral indicators that could be modified by physical activity (PA) in the elderly. Online databases including Pubmed, Web of science (Medline), and Scopus were searched for relevant articles published in the last five years in English. Keywords and combination of these used for the search were the following: "biological", "indicators", "markers", "physical", "activity", and "elderly". Thirty-four papers were analyzed for inclusion. Twenty-nine studies were included and divided into four categories: cardiovascular (CV) biomarkers, metabolic biomarkers, inflammatory markers-oxidative stress molecules, and other markers. There are many distinct biomarkers influenced by PA in the elderly, with promising results concerning the metabolic and CV indexes, as a growing number of studies demonstrate the role of PA on improving parameters related to heart function and CV risk like atherogenic lipid profile. Furthermore, it is also a verified hypothesis that PA is able to modify the inflammatory status of the subject by decreasing the levels of pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α). PA seems also to be able to have a direct effect on the immune system. There is a strong evidence of a positive effect of PA on the health of elderly people that could be evidenced and "quantified" by the modifications of the levels of several biohumoral indicators.

Keywords: physical activity; elderly; biomarkers; noncommunicable diseases; hypertension; diabetes

1. Introduction

Successful aging is one of the main health-related concerns of nowadays, as the public burden related to aging becomes even more consistent, especially in terms of assistance and expense. Physical activity (PA) plays a key role in aging, as many studies have evinced its beneficial effects in primary and secondary prevention of noncommunicable diseases (NCDs) and its influence in the aging process of tissues. Furthermore, PA has a relevant role in mental wellness, in decreasing dementia and stress reactions [1], as well as in increasing the life expectancy. The World Health Organization (WHO) recommends a minimum of 150 min of moderate exercise or 75 min of vigorous training per week for adults, including older adults. Physical inactivity is considered the fourth major risk factor for global

mortality [1], leading to approximately 3 million deaths per year [2]. According to actual data from Europe, there is a lack of active lifestyles in daily life, as older adults spend an average of 9.4 h per day in sedentary activities [3] and only 7% practice regular exercise [1]. Age is indeed the most relevant risk factor for inactivity [4], since for older people, it is significantly more challenging to get engaged in exercise when compared to younger subjects. Conceivably, a comprehensible vicious circle develops, since the presence of systemic diseases prevents the subject from being engaged in exercise and the lack of activity yields a worsening of such systemic pathologic conditions. A major role of physical inactivity has been reported in the onset and worsening of cardiovascular (CV) disease, type 2 diabetes mellitus (T2DM), atherosclerosis, neurodegeneration, and cancer. The combination of these diseases as well as the presence of osteoporosis and sarcopenia configures a frailty syndrome, considered the main cause of disability in the elderly [5].

One of the main challenges of modern medicine and public health is efficient monitoring of health conditions of the elderly to better understand the aging process and to prevent the development of such a vicious mechanism. In the scientific landscape, there is a growing interest in defining the role of several biomolecules and humoral indicators [6] of the aging process and in the modifications of these biomarkers induced by physical activity and exercise [7]. However, the role of PA on these modifications is far from being completely elucidated.

The main objective of the present narrative review is to collect the available evidence above the biohumoral indicators that could be modified by PA in the elderly in order to understand by the use of quantitative indicators its role in protecting the health and functional wellbeing of this age group.

2. Methods

2.1. Criteria for Considering Studies for This Review

Types of studies considered for inclusion in the present review were randomized controlled trials (RCT), prospective cohort studies (PCS), case-control studies (CCS), and letters to the editor. Studies considered should concern biohumoral indicators, biomolecules, and markers that are influenced by PA in elderly.

2.2. Search Methods for Identification of Studies

Online databases including Pubmed, Web of science (Medline), and Scopus were searched for relevant articles published in the last five years in English. Keywords and combination of these used for the search were the following: “biological”, “indicators”, “markers”, “physical”, “activity”, and “elderly”. The studies retrieved were firstly screened by title, and then, the whole abstract was examined for the relevant ones.

After a first selection and exclusion of nonrelevant papers and papers which did not focus on elderly (mean age < 60 years old), the full-text of the potentially eligible articles was retrieved and read for possible inclusion. To enrich the electronic search with further studies, the bibliography of the relevant articles was manually searched to identify potentially eligible papers missed at the electronic search. Thirty-four papers were analyzed for inclusion, 3 of these were then excluded (2 did not concern clinical research, and 1 investigated functional status and not PA). Two more were excluded because they were systematic reviews (Figure 1). Studies included were divided into four categories depending on the type of biohumoral indicators that were investigated: CV biomarkers, metabolic biomarkers, inflammatory markers-oxidative stress molecules, and other markers. The following categories of population were considered by the studies included in the review: community dwelling “healthy” elderly, elderly with pathology/activity limitation, frail elderly, hypertensive patients, diabetic patients, metabolic syndrome patients, and breast cancer patients. After extraction of data concerning the paper, a summary of the results was reported in the text.

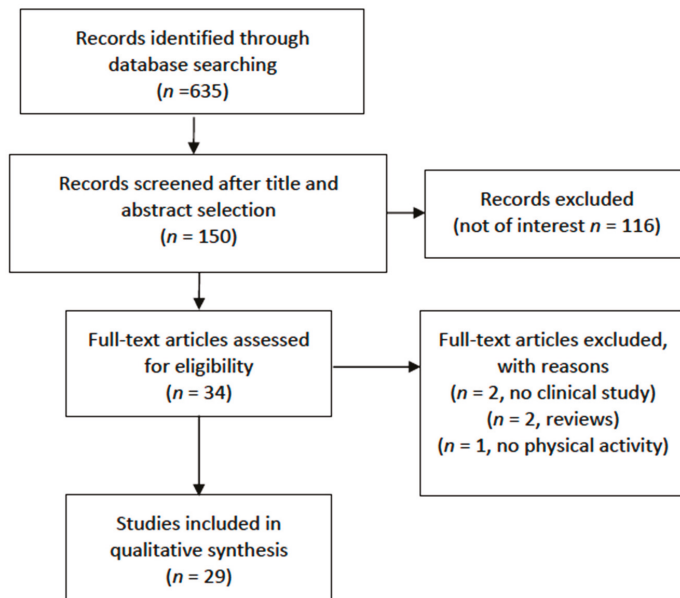


Figure 1. Flow chart of the inclusion process.

3. Results

3.1. Effect of PA on Inflammatory Markers and Oxidative Stress Mediators

It is well known that inflamm-aging, which is an age-related chronic progressive increase in the pro-inflammatory status, plays an important role in the process of aging and age-related conditions like cognitive decline and chronic comorbidities [8,9]. Several research studies evidenced that healthy aging could be related both to a lower pro-inflammatory status and to an efficient anti-inflammatory response. The imbalance between these two pathways can be a risk factor for frailty and chronic age-related pathologies leading to poor quality of life [10]. Oxidative stress occurs from the imbalance between the production of reactive oxygen and nitrogen species (RONS) and the antioxidant defences. It has been hypothesized that oxidative stress could have a role in the aging process as the age-related modifications could be caused by the accumulation of RONS-induced damages that lead to a progressive loss of function in tissues and organs [11]. Several research studies have investigated the influence of PA on inflammatory and oxidative stress biochemical markers in the elderly. It has been demonstrated that an active lifestyle can influence the age-related inflammatory profile [12], reducing the secretion of pro-inflammatory factors and increasing the release of anti-inflammatory cytokines. Nevertheless, the effect of different type and intensity of exercise on these pathways has not been fully clarified yet. Monteiro-Junior et al. performed a systematic review and meta-analysis on studies investigating the effect of chronic exercise on interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive Protein (CRP) in a population of ≥ 60 elderly persons (8 articles were analyzed after screening and application of inclusion/exclusion criteria) [13]. IL-6 and CRP but not TNF- α significantly decreased after the exercise intervention (overall effect $p < 0.05$). A systematic review by Cronin et al. investigated the effect of aerobic and resistance exercise on inflammatory markers (CRP, IL-6, interleukin-8 (IL-8), interleukin-1 beta (IL-1 β), and TNF- α) in healthy, physically inactive subjects (11 articles included). Results from studies investigating an elderly population (3 studies of the 11) showed the greatest reduction of inflammatory markers (CRP and IL-6), while results from studies including younger subjects were inconsistent. These different results in the different age groups are probably due to

higher basal level of these markers in the elderly and to the resulting higher potential for them to be lowered by PA in this population [14]. Another cross-sectional study investigated the association between inflammatory markers (IL-6 and soluble receptor for TNF- α (sTNFR1)) and muscle/functional performances (assessed by 10 m gait speed) in 221 community-dwelling elderly women aged of ≥ 65 years. Results did not show any negative correlation between levels of IL-6 and sTNFR1 and muscle or physical performance, probably because the levels of these mediators were not high enough to influence muscles and functionality of the sample [15]. A cross-sectional (1139 subjects included) and longitudinal study (490 subjects with two measures of PA one year apart were included) on elderly men [16] investigated the influence of different levels of PA and sedentary behaviour (SB) on markers of inflammation (IL-6, CRP, and tissue plasminogen activator (tPA), von Willebrand factor (vWF), D-Dimer (ng/mL), and insulin-like growth factor-1 (IGF-1)). PA and SB were measured using Actigraph GT3X accelerometers. Results showed that the individuals who spent more time in Moderate to Vigorous PA (MVPA) had lower levels of IL-6, CRP, tPA, vWF, and D-dimer and higher levels of IGF-1 ($p \leq 0.006$) in contrast with men with higher levels of SB that resulted in having higher levels of IL-6, CRP, tPA, and D-dimer and lower levels of IGF-1 ($p \leq 0.03$). Moreover, each additional 10 min of MVPA showed to have a lowering effect on IL-6, CRP, tPA, vWF, and D-dimer (3.2%, 5.6%, 2.2%, 1.2%, and 1.8% respectively) that, for CRP, vWF, and D-dimer, was independent from levels of SB. A cross-sectional study performed by Do-Yeon et al. [17] investigated the association of quality of diet and physical performance assessed by the Short Physical Performance Battery (SPPB) with IL-6 and TNF- α in 78 frail, elderly South Korean individuals aged ≥ 65 years. The results evidenced that high physical performances (as assessed by SPPB) were associated with lower levels of TNF- α ($p = 0.001$).

Plasma levels of IL-6 and TNF- α were also measured in a population of elderly subjects with hypertension undergoing aerobic training or aerobic and resistance training for 10 weeks. In the group of subjects that underwent both aerobic and resistance training, TNF- α levels were lower ($p = 0.01$), while IL-6 was reduced in subjects undergoing aerobic training compared to untrained controls ($p = 0.04$) [18]. Moreover, direct measurement of the levels of oxidative products has been carried out in some studies. Alghadir et al. showed that, in a population of elderly undergoing a 24-week program of PA, there was a significant decrease in oxidative stress markers, including high sensitivity C-reactive protein (hsCRP), malondialdehyde (MDA), and 8-hydroxyguanine (8-OHdG) when compared to subjects who did not exercise [19]. Similarly, a 12-week program of Nordic walking in elderly women showed a decrease in levels of MDA oxidation products ($p = 0.01$) [20]. In another study, a thorough evaluation of the oxidative status of the included subject (61 women and 34 men aged ≥ 60 years) was carried out through determination of plasma total antioxidant status (TAS), plasma antioxidant enzyme activities, i.e., glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD), and membrane lipid peroxidation (TBARS). Accelerometers were used to evaluate PA. Among the female sample, TAS was significantly lower and CAT activity was significantly higher in the group that met the criteria of recommended levels of PA for healthy adults (daily step goal of 10,000 steps) than in the group that did not meet these criteria. Correlation analysis showed an inverse association between PA and TAS, while moderate to vigorous physical activity (MVPA) was related to an increase in GPx antioxidant activity in the elderly women sample. In elderly male subjects, a significant correlation was found between CAT activity and the level of PA related to the lifestyle [21]. On the same research line, in a large study involving 1449 subjects, SOD activity and plasma levels of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) were determined. Results from a subpopulation of elderly subjects with hypertension showed that different types of PA induced an improvement in antioxidant activity and a reduction in MDA levels; however, these results were not always significant for all the types of PA advocated [22]. Other direct markers of inflammation are those related to the activation of the immune system, including the toll-like receptor (TLR) on white blood cells. This marker has been investigated in a clinical trial, evaluating the effect of an 8-week program of resistance training in elderly subjects. Results showed that, in those patients that completed the program, the expression of TLR-2 and TLR-4 was reduced ($p < 0.04$ and $p < 0.03$, respectively). Furthermore, C-reactive protein

levels also decrease in the training group [23]. Similarly, another trial by the same research group demonstrated that whole-body vibration training had a significant effect in the reduction of TLR-2 and TLR-4 in a population of elderly subjects [23]. Furthermore, a cross-sectional study which evaluated TLR activity and cytokines expression reported results stratified by Metabolic Equivalent of Tasks (MET), showing that elderly subjects with higher MET levels and exercise levels had decreased blood levels of IL-6 ($p = 0.001$) but not of TNF- α ($p = 0.148$) and myeloperoxidase ($p = 0.799$). TLR-2 levels significantly decreased both in males and females, according to MET levels, while TLR-4 did not show any significant decrease [24]. Results of the included studies were reported in Table 1.

Table 1. Inflammatory markers and oxidative stress mediators.

Study	Physical Activity	Participants	Biomarkers	Main Findings
Alghadir et al. 2016 [19]	Moderate aerobic for 24 weeks	100 (age 65–95 y)	MDA, 8-OHdG, TAC, and hs-CRP	Physically active persons showed a higher cognitive performance along with reduction in the levels of MDA, 8-OHdG, and hs-CRP and increase in TAC activity compared with sedentary participants.
Felicio et al. 2014 [15]	Muscle performance and handgrip were measured using dynamometer	221 women (mean age 71 y)	IL-6, SNTFR	IL-6 (0.87 pg/mL) correlated with the power of the knee extensors ($r = 0.14$; $p = 0.03$) and the power of the knee flexors ($r = 0.16$; $p = 0.01$). IL-6, level of physical activity, and depressive status explained 5.5% ($R^2 = 0.055$, $p < 0.01$) of average power of knee extensors variability.
Ferrer et al. 2018 [24]	Metabolic equivalent of task measurement; Minnesota leisure-time physical activity level	116 (age 55–80 y)	IL-6 and TLR protein array	Exercise induced a decrease in the IL-6 circulating levels and the TLR2 protein levels in PBMCs. Anti-inflammatory IL-10 was increased in active subjects.
Fraile-Bermudez et al. 2015 [21]	Level of physical activity measured through accelerometers	61 women and 34 men (mean age 70 y)	GPx, SOD, CAT, and TBARS	In active women, lower levels of TAS were found. Moderate to vigorous physical activity was negatively correlated with TAS but was correlated with increase in the GPx activity. The counts per minute were positively correlated with CAT activity.
Kim et al. 2017 [17]	Grip strength and SPPB	78 (mean age 78.3 y)	IL-6 and TNF- α	Higher SPPB score was associated with lower levels of TNF- α .
Kortas et al. 2017 [20]	Nordic walking for 12 weeks	35 women (mean age 68 y)	MDA and AOP	Statistically significant decreasing of MDA level and concentration of AOP
Lima et al. 2015 [18]	Aerobic training vs. aerobic + resistance training for 10 weeks	44 (age 60–75 y)	IL-6 and TNF- α	IL-6 was reduced in aerobic training group compared to controls ($p = 0.04$), and TNF- α levels were lower in aerobic + resistance group compared to controls ($p = 0.01$).
Mendoza-Nunez et al. 2018 [25]	Tai-Chi	110 affected by MetS	TAS, TNF- α , IL-6, IL-8, and IL-10	Activity group showed a statistically significant increase in TAS and a decrease in the oxidative stress score ($p < 0.05$).
Parsons et al. 2017 [16]	Level of physical activity measured through GT3X accelerometers	1139 (mean age 79 y)	IL-6, CRP, tPA, vWF, and D-Dimer	Higher physical activity was associated with lower levels of IL-6, CRP, tPA, vWF, and D-Dimer. Furthermore, each additional 10 min of moderate to vigorous activity was associated with a 3.2% lower IL-6, 5.6% lower CRP, 2.2% lower tPA, 1.2% lower vWF, and 1.8% lower D-dimer.

Table 1. Cont.

Study	Physical Activity	Participants	Biomarkers	Main Findings
Rodriguez-Miguel et al. 2014 [23]	Resistance exercise training	26 (mean age 69.5 y)	IL-10, TNF- α , and CRP	TNF- α remained unchanged in both trained subjects and controls. IL-10 was upregulated in trained subjects. CRP values decreased in trained subjects only.
Yu et al. 2018 [22]	Walking, square dancing, Taiji, and yoga	1449 (age 45–79 y), with or without hypertension	SOD, MDA, and 4-HNE	In individuals with hypertension, MDA levels decreased (if walking/square dancing), SOD activity increased (if walking/square dancing), and 4-HNE levels decreased (if Taiji/yoga). In individuals without cardiovascular disease, MDA levels decreased (if any activity), SOD activity increased (if walking/square dancing), and 4-HNE levels decreased (if Taiji/yoga)

Where not specified, the patients were healthy community-dwelling elderly subjects. MDA = malondialdehyde, 8-OHdG = 8-hydroxyguanine, TAS = Total Antioxidant Status, TAC = Total Antioxidant Capacity, and hs-CRP = high-sensitivity C-reactive Protein, MetS = Metabolic Syndrome, tPA = tissue plasminogen activator, vWF = von Willebrand factor, SNTFR = soluble receptor for tumor necrosis factor alpha, AOP = advanced oxidation products, SPPB = Short Physical Performance Battery, GPx = glutathione peroxidase, CAT = catalase and SOD = superoxide dismutase, TBARS = membrane lipid peroxidation, PBMC = peripheral mononuclear blood. Cells, 4-HNE = hydroxynonenal, y = years, TLR = toll like receptor, IL = interleukin-1, TNF- α = tumor necrosis factor-alpha, CRP = C-reactive Protein.

3.2. Effect of PA on Cardiac Biomarkers

A sedentary lifestyle and the lack of a scheduled activity during daily life are well-established risk factors for cardiovascular disease (CVD) because of negative effects on cardiac and endothelial function, including a pro-atherogenic action [26,27]. The classical and nonclassical risk factors for CV disease were investigated in a recent paper, where the single factors were measured at different time-points of a specific PA program in a sample of elderly women (aged 65.0 ± 7.3 years). Body mass index (BMI), waist and hip circumferences, resting systolic and diastolic blood pressure (BP), and resting heart rate were significantly reduced after 2 weeks of a program based on general fitness, yoga, body balance, and self-guided PA. Exercise capacity, low-density lipoprotein (LDL) and high-density lipoprotein (HDL-C), cholesterol, and other atherogenic lipid indices (ALI) also improved after 2 weeks. At three months of the PA program, the values of these markers improved even more, with a significant reduction of calculated CVD risk at ten years [1]. PA also stimulates endothelium to synthesize and release the tissue-plasminogen activator (tPA), and some evidence suggested that also E-selectin may be influenced by PA [26]. A plethora of factors are actually influenced by PA, including C-reactive protein (CRP), interleukin-6 (IL-6), tPA, E-selectin, and adipokines, and several studies attempted to address the influence of PA on the cardiovascular system. A recent paper by Elhakeem et al. evaluated heart rate and data collected by movement sensors to derive overall PA energy expenditure (KJ/kg per day) and time spent in sedentary behaviours (<1.5 metabolic equivalent of tasks), in light PA (1.5–3 metabolic equivalent of tasks), and in moderate-to-vigorous intensity PA (>3 metabolic equivalent of tasks). Results of the linear regressions analysis showed a significant association between time spent in PA (both in light and moderate to vigorous) and blood levels of CRP, IL-6, leptin, and adiponectin, especially in women [26]. Furthermore, the same study reported a positive association between cardiorespiratory fitness and favourable biomarkers levels. Among other biomarkers, a recent cross-sectional study on 1130 men evaluated the influence of PA on the behaviour of N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity Troponin T (hsTnT), which are both markers of cardiac injury. The results showed that the total amount of PA in patients aged 70–91 years was nonlinearly associated to lower NT-proBNP and hsTnT. Higher levels of PA were associated with lower levels of NT-proBNP but significantly only below a certain threshold of activity per day (measured by accelerometer count, step count, and minutes of moderate/vigorous activity). Similarly,

PA level was also associated with lower levels of hsTnT, with significant correlations only below threshold levels of counts, steps, moderate/vigorous activity, and light activity [16]. On the same research line, Van der Linden et al. hypothesized that the frail elderly population is characterized by high levels of basal cardiac Troponin T (cTnT) and may benefit from the potential effects of an exercise intervention. The greatest part of the population evaluated had cTnT levels above the 99th percentile. However, results showed no evident effect of a 24-week resistance-training program on the cTnT levels [28]. Results of the included studies were reported in Table 2.

Table 2. Cardiovascular risk biomarkers.

Study	Type of Exercise	Participants	Biomarkers	Main Findings
Elhakeem et al. 2018 [26]	Light and moderate-to-vigorous activity, monitored with sensors worn for 5 consecutive days	795 men and 827 women (age 60 to 64 y)	E-selectine, leptin, and adiponectine	Greater time in light PA and moderate-to-vigorous intensity PA and less sedentary time were associated with more favorable biomarker levels.
Koh et al. 2018 [29]	Aerobic capacity (VO ₂), physical activity frequency, intensity, and duration	141 (mean age 70.6 y)	Ecographic and cardiac magnetic resonance imaging parameters	Compared to participants with high VO ₂ , participants with low VO ₂ had lower ratio of peak velocity flow in early diastole to peak velocity flow in late diastole by atrial contraction of >0.8 ($p = 0.001$) and lower left atrial conduit strain ($p = 0.045$)
Parsons et al. 2018 [16]	Level of physical activity measured through GT3X accelerometers	1130 men (age 70 to 91 y)	NT-proBNP and hsTnT	For each additional 10 min of moderate/vigorous activity, NT-proBNP was lower by 35.7% and hsTnT was lower by 8.4%, in men who undertook <25 or 50 min of moderate/vigorous activity per day, respectively.
Van der Linden et al. 2014 [28]	24-week supervised resistance-type exercise training program vs. normal activity monitoring	52 pre-frail elderly (age ≥ 65 y)	cTnT	The majority of participants had cTnT levels above the 99th percentile. These data confirm the hypothesis that chronically elevated cTnT concentrations are highly prevalent among (pre)frail elderly subjects.
Zmijewski et al. 2015 [27]	Organized, group-based physical activity	35 women (mean age 65 y)	BP, resting HR, EC, HDL, and LDL	Two-week effects included significant decreases in BMI, waist and hip circumferences, resting BP, and resting HR; improved EC; and improved LDL, HDL, and TC, with a reduction in 10-year estimated risk of death from CVD. Three-month effects included a further decrease in systolic BP, improvements in EC and HDL, and maintenance of lower levels of CVD risk.

Where not specified, the patients were healthy community-dwelling elderly subjects. PA = physical activity, TC = Total Cholesterol, TAG = triacylglycerols, HDL = High-Density Lipoproteins, LDL = Low-Density Lipoproteins, BP = blood pressure, HR = heart rate, EC = exercise capacity, BMI = Body Mass Index, CVD = Cardiovascular Disease, NT-proBNP = N-terminal pro-brain natriuretic peptide, hsTnT = high sensitivity Troponin T, cTnT = cardiac Troponin T.

3.3. Effect of PA on Metabolic Parameters

There is a consistent and rising evidence that metabolic pathways and endocrine system as well as immune system and defense mechanisms are definitely affected by the aging process. Specifically, in the elderly, the carbohydrates metabolism is impaired and utilization of blood glucose is decreased [30]; furthermore, in this population, lipid profile results were imbalanced by the altered fat utilization and the lack of PA [31]. Vitamin D levels, the main factor influencing bone health, also result in impairment for a plethora of alterations in kidney and other endocrine organs [32]. There is a growing interest

and development of new data analysis methods for the assessment of metabolic status and metabolic changes that occur in the individual during and after activities [33]. It is a common hypothesis that the prevention of metabolic noncommunicable diseases passes through the opportunity to understand which kind of activities may be useful in improving the metabolome of the elderly. In a recent study based on aged Korean woman, the effect of combined aerobic and anaerobic exercise on glucose metabolism was investigated by assessing insulin resistance, Growth Hormone (GH), Insulin-like growth factor-1 (IGF-1), Deidrossiepiandrostenedione (DHEA-S), and estrogen values. The authors found that blood glucose levels decreased significantly when compared to non-exercise controls while GH and DHEA-S increased. Interaction effects were found for IGF-1, GH, and DHEA-S. From these results, it seems that, in older women, the combination of aerobic and anaerobic exercise improves insulin resistance, avoiding the decline of glucose metabolism function [30]. Combined exercise was also investigated in another study; specifically, the effect of resistance training and multicomponent exercise was compared. Main findings included the evaluation of aerobic functionality, lipid profile, and inflammatory markers. The results showed that only epidermal growth factor (EGF) levels and adiponectin (ADN) levels were different between groups, with an increase of the EGF in the group of elderly undergoing multimodal fitness program and a significant ADN reduction in the resistance training group [31]. In a study carried out on 85 healthy older subjects, the levels of vitamin D, creatinine kinase, lactic acid dehydrogenase, troponin I, total antioxidant capacity, body composition, and PA were evaluated to find possible correlations among these parameters. Main findings showed that, in physically active subjects, there was a significant increase in the vitamin D serum levels, calcium, and total antioxidant capacity, with an associated reduction in the levels of muscle fatigue biomarkers: creatine kinase, lactic acid dehydrogenase, troponin I, and hydroxyproline. Based on these results, improved biohumoral markers of bone and muscle health correlated with the improvement in muscle relief and performance of physically active participants [32]. Similarly, a study investigating the beneficial effects of Tai-Chi in older adults showed a statistically significant difference in glycosylated haemoglobin levels compared to untrained controls as well as a significant increase in total antioxidant status [25]. Another study evaluating the association between peak oxygen uptake (a marker of aerobic capacity) and metabolic/cardiovascular parameters showed that subjects with lower VO_2 had a higher risk to present altered cardiovascular parameters and had higher levels of accumulation of wide-spectrum acyl-carnitines, alanine, and glutamine [29]. The role of microRNA in diabetes mellitus type 2 (T2DM) is growing in interest in the scientific literature. Reduced levels of the microRNAs miR-146a and miR-155 contribute to a pro-inflammatory state associated with T2DM. The effect of strength and cardiovascular training on T2DM patients has been investigated compared to a group of nondiabetic subjects, showing a significant increase of miR-146a and a decrease of blood glucose levels, which were more pronounced in diabetic patients after strength training [34]. In a Swedish study aimed at evaluating the wellbeing of the elderly, the Psychological General Wellbeing (PGWB) index has been put into correlation with several metabolic biomarkers, including the levels of several types of lipoproteins, BMI, and blood pressure. The only significant results found was a positive association between the high-density lipoprotein and the level of general health, according to the PGWB [35]. Caminiti et al. investigated hormonal responses (levels of total and free testosterone, IGF-1, GH, and Sex-Hormone binding protein (SHBG)) after two different types of aerobic PA (interval training (IT) and continuous training (CT)) in chronic heart failure (CHF) elderly patients. Results showed a greater increase in total and free testosterone levels and in IGF-1 in the IT group compared to the CT group. On the contrary, levels of testosterone and IGF-1 remained unchanged after CT. GH significantly increased and SHBG decreased in both groups without between-groups differences. The level of hormonal response was related neither to an improvement of exercise capacity nor to the training load, but it seemed to be related to exercise intensity [36]. Results of the included studies were reported in Table 3.

Table 3. Metabolic biomarkers.

Study	Type of Exercise	Participants	Biomarkers	Main Findings
Al-Eisa et al. 2016 [32]	Physical activity assessed through estimated energy expenditure scores	85 (age 64 to 96 y)	TAG, TC, LDL, HDL, 25(OH)D, TAC, CK, LDH, Troponin I, and hydroxyproline	Significant reduction of TC, TAG, LDL, and HDL occurred in subjects with moderately active and active subjects. Significant increase in 25(OH)D and TAC and a reduction in the levels of muscle fatigue biomarkers occurred in physically active subjects.
Biddle et al. 2018 [33]	Physical behaviors (time spent per day): stepping, sleeping, sitting, and standing	435 (mean age 66.7 y)	Fasting and 2 h glucose and insulin levels, and HbA1c	Reallocating 30 min from sleep, sitting, or standing to stepping was associated with 5–6 fold lower 2-h glucose, 15–17 fold lower 2-h insulin, and higher insulin sensitivity.
Ha and Son 2018 [30]	Aerobic + anaerobic exercise for 12 weeks vs. controls	20 Korean women	Insulin resistance, GH, IGF-1, DHEA-S, and estrogen	GH level increased significantly in the exercise group. The DHEA-S level significantly increased in the exercise group. The estrogen level increased significantly in the exercise group.
Hurtig-Wennlof et al. 2014 [35]	International Physical Activity Questionnaire modified for the elderly.	389 community-dwelling elderly (mean age 74 y)	LDL, HDL, Apolipoprotein A1, and B. PGWB	PGWB correlated significantly with all parameters, positively with LDL, HDL ApoA1 (respective Spearman's rho 0.03, 0.05, and 0.013), and negatively with ApoB (rho -0.031).
Kortas et al. 2017 [20]	Nordic walking for 12 weeks	35 women (mean age 68 y)	TC, TAG, HDL, LDL, and ferritin	The training induced a rise of HDL cholesterol ($p < 0.05$), whereas other lipid parameters remained unchanged. Decrease of blood ferritin ($p < 0.05$)
Leite et al. 2015 [31]	Resistance training vs. multicomponent exercise for 12 weeks	24 women and 15 men (age 65 to 75 y)	LDL, HDL, glucose, TAG, NEFA, adiponectine, ferritin, and EGF	Among the evaluated biomarkers, only high molecular weight adiponectin decreased significantly within the RT group ($p = 0.03$) after the exercise protocol. Between-group differences included only ferritin ($p = 0.02$) and EGF ($p = 0.01$).
Mendoza-Nunez et al. 2018 [25]	Tai-Chi	110 affected by MetS	HbA1c	Decrease in HbA1c concentration was observed in the TC group compared with the control group ($p < 0.05$).
Santos Morais et al. 2017 [34]	Strength training and guided walk (monitored through Polar Team software)	23 (mean age 68.2 y), of whom 13 were diabetics	miR-126, miR-146a, and miR-155 in	Diabetic patients had higher reduction in blood glucose than nondiabetics, which was paralleled by a positive change of the circulating levels of miR-146a but not of the other miRs.

Where not specified, the patients were healthy community-dwelling elderly subjects. MetS = Metabolic Syndrome, TC = Total Cholesterol, TAG = triacylglycerols, HDL = High-Density Lipoproteins, LDL = Low-Density Lipoproteins, HbA1c = glycosylated haemoglobin, GH = growth hormone, IGF-1 = Insulin-like Growth Factor 1, DHEA-S = dehydroepiandrosterone sulphate, NEFA = Non Esterified Fatty Acid, EGF = Epidermal Growth Factor, 25(OH)D = 25-hydroxy vitamin D, TAC = Total Antioxidant Capacity, CK = Creatinine Kinase, LDH = Lactic acid DeHydrogenase, VO₂ = peak Oxygen Uptake, PGWB = Psychological General Wellbeing, miR = micro RNA.

3.4. Effect of PA on Other Biohumoral Markers

A plethora of other biomarkers has been investigated to understand and highlight the effect of PA on their levels. In a cohort of postmenopausal women with breast cancer, the levels of progesterone, estrogens, and their precursors were measured on tissue samples and correlated to BMI and PA status. An interesting result is that estradiol, estrone, and testosterone levels were significantly associated with BMI in women with Estrogen Receptor positive (ER+) breast cancer. Furthermore, an inverse association was found between time spent in PA and serum estradiol levels among ER+ subjects, although this difference was not significant on tissue samples [37]. Another relevant biomarker that has been recently proposed as a predictor of changes in physical function is the C-terminal Agrin Fragment

(CAF), a product of the catabolism of neuromuscular junction molecule Agrin. A cohort of 333 older subjects has been followed for 1 year to evaluate the effect of a 12-month program of health education only or a 12-month program of walking, strengthening, flexibility, and balance exercises. However, the large trial failed to demonstrate a significant association between CAF levels and the 12-month activity program [38]. Two large studies investigated the role of PA on kidney function. A study on 1041 older subjects investigated the association between muscular strength and kidney dysfunction, by measuring cystatin C levels and maximal muscle strength. The odds ratio of having elevated cystatin C was higher in those subjects with lower muscle strength. Similarly, those subjects with lower muscle strength had also lower estimated glomerular filtration rate from cystatin C (eGFR_{cysC}) [39]. The second study evaluated a cohort of 1352 men, in which the higher levels of PA and lower levels of sedentary behaviours reduced the odds ratio for decreased eGFR [16]. Moreover, a recent paper investigated the possible role of PA on renal proximal tubule stress levels through the evaluation of urinary levels of liver-type fatty acid-binding protein (L-FABP). The intent of the study was two-fold: in a cross-sectional evaluation, urinary L-FABP levels were significantly lower in those subjects with higher PA levels than in those with lower PA levels; in the interventional study, those subjects that underwent 12 weeks of aerobic training had significantly decreased levels of urinary L-FABP [40].

4. Discussion

There is growing evidence on the effects of PA in the elderly, and the clinical tools for the assessment of these effects are the focus of several recent research studies. According to the results of the present review, there are many distinct biomarkers influenced by PA in the elderly, although none of them have sufficient evidence for clinical use as the majority of these biomolecules have been investigated in one or very few studies. However, promising results are available, especially concerning the metabolic and cardiovascular indexes, as a growing number of studies demonstrate the role of PA on improving parameters related to heart function and CV risk like atherogenic lipid profile [41]. Prospective observational studies confirm that high–moderate levels of leisure time PA are able to decrease the risk of CV disease in both sexes with an effect size that ranges between 20–30% and 10–20% respectively, showing a dose–effect relationship [41]. Research studies have evidenced that the association between higher levels of PA and lower CV disease rates can be explained in large part by the reduction of known risk factors, with inflammatory/hemostatic biomarkers making the largest contribution to lowered risk, followed by a positive effect on blood pressure, lipids, and body mass index [42]. Furthermore, it is also a verified hypothesis that PA is able to modify the inflammatory status of elderly subjects by decreasing the levels of pro-inflammatory cytokines, including IL-1, IL-6, and TNF- α [13,14]. Several studies have investigated the effect of exercise on inflammatory factors; it has been evidenced that acute bouts of exercise result in a transient, mostly pro-inflammatory effect, which is proportional to the amount of exercise and to the entity of muscle injury [43,44]. On the other hand, regular PA has been associated with a chronic anti-inflammatory effect. The mechanisms underlying this action are not well defined and include reduction of body weight [45], reduction of basal levels of pro-inflammatory cytokines and pro-atherogenic adipokines, enhancement of the expression of antioxidant and anti-inflammatory mediators in the vascular wall, and insulin-sensitizing pathways [46,47]. Moreover, regular exercise has been demonstrated to be able to attenuate the age-associated increase in oxidative stress and nuclear factor- κ B activation in animals [48] and to reduce toll-like receptor signaling [23], which may explain its chronic anti-inflammatory effect.

As for the influence of PA on oxidative stress and antioxidant systems, a recent review by Nocella et al. [7] highlighted that high-intensity physical exercise can cause redox imbalance, leading to several types of injuries and muscle damage, while the studies reported in this review show an improvement in antioxidant activity and reduction of oxidative stress in elderly performing regular PA. Similar to our results, some studies demonstrated that exercise and regular PA have a positive impact on oxidative stress and inflammation during aging [49,50]. The balance between Reactive oxygen species (ROS) production and antioxidant systems is a very important, as ROS plays a dual role: at low or moderate

levels, they have a beneficial action on cellular responses, while at high concentrations, they cause inflammation and oxidative damage to cells and tissues [51,52]. This is crucial for the aging process, as inflammatory processes and oxidative stress are biochemical alterations related to the etiology and complications of several age-related diseases such as T2DM, Alzheimer's disease, CV disease, and cancer. It has been evidenced that regular practice of PA has a positive effect on the aging process, with an action on biochemical changes related to aging and on the risk of chronic diseases. This action has the consequence of enhancing quality of life in aging individuals and of increasing longevity [53,54]. It has also been evidenced that PA could modify blood glucose levels and glycosylated haemoglobin levels in nondiabetic elderly subjects [42]. One study has also demonstrated a significant increase in miR-146a (reduced concentrations of miR-146a contribute to a pro-inflammatory state associated with T2DM) with a decrease in serum blood glucose levels, which was more evident in the group of diabetic patients compared to healthy individuals after strength training [34]. In agreement with our results, literature shows that PA (both endurance and strength training) has an important role in the prevention and control of T2DM, producing acute and chronic physiological effects [55,56]. It has been demonstrated that insulin action in muscle and liver can be modified by acute bouts of exercise and by regular PA. Regular training increases muscle capillary density and insulin signaling proteins [57]. Moreover, it has been evidenced that both aerobic and resistance training promote adaptations in skeletal muscle, adipose tissue, and liver associated with enhanced insulin action, regardless of weight loss [58].

Some studies reported in this review showed that PA was able to raise testosterone, GH, and vitamin D levels in elderly populations [32]. Our results comply with the results of some cross-sectional studies performed on middle-aged and older men which indicate that circulating testosterone concentrations may be higher in men who regularly exercise [59,60], and this is very important in the elderly in order to counteract the physiological age-associated decline of serum testosterone. It should be noted that low levels of testosterone in men have been associated with decreased sexual function, loss of muscle mass and strength, osteoporosis, declining cognitive function, and poorer quality of life [61]. As for the effects of PA on GH levels, neuroendocrine mechanisms underlying exercise-facilitated GH secretion are complex; they probably include somatostatin withdrawal, GH-releasing hormone (GHRH) release, and possibly co-secretagogue actions. The effect of PA on vitamin D levels could be related to the evidence that shows that long-term regular exercise programs are able to increase bone mineral density (BMD) in the elderly and to consequently reduce the risk of osteoporotic fractures [62], which are the most fearsome events in an aged person that frequently lead to disability, hospitalization, and death.

There is also some evidence from literature about the role of PA on other interesting markers like CAF and urinary L-FABP [40], but further studies should be designed to confirm and fully explain these results.

Concerning the kind of exercise that could have a positive effect on health indicators in the elderly, there is not strong evidence, as the majority of the studies in literature have focused on global levels of PA. Only a few of them investigated the effect of aerobic, resistance or combined training, or specific kind of activities (Tai-chi, Nordic walking, and whole-body vibrations) on biohumoral indicators. Well-designed clinical trials on the effect of a different kind of PA on health indicators are therefore needed to better understand the role of each kind of exercise on specific physiopathological pathways.

Moreover, most of the reported studies investigate a population of "healthy" community-dwelling elderly and only a few of them include people with chronic pathologies (Tables 1–3). This scarce evidence on elderly with chronic comorbidities limits the transposition of the results to clinical settings in which the majority of the individuals have multimorbidity [63].

5. Conclusions

The studies that are reported in this review give strong evidence of an effect of PA on the health of elderly people that is not generic and confused but could be evidenced and "quantified" by the modifications of the levels of biohumoral indicators. This represents an additional support

to the concept of the role of PA in primary and secondary prevention of noncommunicable diseases. Therefore, the practice of PA and the reduction of sedentary behaviors should be encouraged in all ages, overcoming psychological barriers and false beliefs of the elderly. The evidence coming from further clinical research and new biotechnologies could help in having the opportunity to “tailor” the right type of exercise for the particular clinical and genetic features of each individual in order to build up an individualized preventive strategy.

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Review

Physical Activity for the Treatment of Chronic Low Back Pain in Elderly Patients: A Systematic Review

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Abstract: Chronic low back pain (CLBP) affects nearly 20–25% of the population older than 65 years, and it is currently the main cause of disability both in the developed and developing countries. It is crucial to reach an optimal management of this condition in older patients to improve their quality of life. This review evaluates the effectiveness of physical activity (PA) to improve disability and pain in older people with non-specific CLBP. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used to improve the reporting of the review. Individual risk of bias of single studies was assessed using Rob 2 tool and ROBINS-I tool. The quality of evidence assessment was performed using GRADE analysis only in articles that presents full data. The articles were searched in different web portals (Medline, Scopus, CINAHL, EMBASE, and CENTRAL). All the articles reported respect the following inclusion criteria: patients > 65 years old who underwent physical activities for the treatment of CLBP. A total of 12 studies were included: 7 randomized controlled trials (RCT), 3 non-randomized controlled trials (NRCT), 1 pre and post intervention study (PPIS), and 1 case series (CS). The studies showed high heterogeneity in terms of study design, interventions, and outcome variables. In general, post-treatment data showed a trend in the improvement for disability and pain. However, considering the low quality of evidence of the studies, the high risk of bias, the languages limitations, the lack of significant results of some studies, and the lack of literature on this argument, further studies are necessary to improve the evidences on the topic.

Keywords: chronic low back pain; elderly; old aged patients; physical therapy; physical activity; walking; global postural rehabilitation; cycling; hydrotherapy; yoga

1. Introduction

Low back pain (LBP) is a common symptom that can improve spontaneously within a few weeks. However, about 2–7% [1] of cases may evolve into chronic low back pain (CLBP) that may lead to significant disability. Age is a well-known risk factor for CLBP in association to [2,3], psychological distress, inactivity, social environment, comorbidity, gender, genetic, and prior work exposure. CLBP affects approximately 20–25% of the elderly population (older than 65 years) [4], and it currently is the main cause of disability both in the developing and developed countries [5,6]. It increases linearly from the third decade of life affecting more women than men [7]. After a single episode of LBP, there is a higher risk to become recurrent [8]. CLBP, that is one of the most important conditions that leads to work-related disability, has dramatic consequences on the costs for the health system [9]. It is defined by the location of pain between the lower rib margins and the buttock that lasts for more than 12 weeks [10,11] and it can be often accompanied by neurological symptoms in the lower limbs (i.e., sciatica). Causes of CLBP can be distinguished into specific (degenerative process to the spinal

segments of the lumbar spine such as lumbar spinal stenosis, spondylolisthesis, or disc herniation) [12] or non-specific, apparently when there is no underlying source of pain [13]. Among patients affected by LBP in primary care, patients affected by CLBP represent the greatest part (over 85%) [14]. CLBP in older adults has multifactorial causes, including both biological (insufficient muscle function around the spine [15]), and psychosocial factors [16] and, especially in the older adults it can lead to a severe reduction of independence and performance of normal daily activities [17].

Thus, it is crucial to reach an optimal management of this condition in older patients in order to improve their quality of life. However, limited evidence is available about the effectiveness of commonly recommended treatments for the older patient with CLBP. Paecq et al. showed that only a few clinical trials published in the literature were focused on older people. In fact, most studies include people younger than 65 years [18]. However, not all treatment options normally indicated for young people can also be pursued in the elderly population, since there may be other comorbidities, such as osteoporosis, that can limit their applicability.

Clinical practice guidelines for CLBP recommend physical activity (PA) as one of the most used interventions based on its biological rationale [19] and since it is easily applicable and low cost [20–22]. PA improves functions, mobility, quality of life, and some psychological distress that can be often found in older adults. Moreover, PA can improve social and work participation, coping strategies, and reduces fear-related beliefs regarding CLBP [23]. In the same way, physical inactivity is significantly correlated with the worsening of several chronic conditions including type 2 diabetes mellitus, congestive heart failure, and cognitive disorders such as depression and neurodegenerative diseases [24]. Therefore, PA can be useful and have positive effects on older patients with CLBP and other chronic conditions [25].

In the current review, PA is defined as a supervised activity program including general physical fitness programs, total body cardiovascular exercises, back schools, and specific techniques aimed at increasing single muscle strength or stretching such as Pilates, McKenzie, Feldenkrais, Tai Chi, or aquatic physiotherapy/hydrotherapy. The aim of this systematic review is to evaluate the effectiveness of PA in improving disability and pain in elderly patients with non-specific CLBP, comparing the results with groups of patients treated through manual therapy and other therapies that include non-physical intervention (advice to keep active) and untreated groups.

2. Materials and Methods

We focused our research on studies concerning PA as a treatment for CLBP in elderly patients. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used to improve the reporting of the review. The Grading of Recommendations Assessment Development and Evaluation (GRADE) [26] approach was used to assess the quality of evidence of the articles that include full data.

2.1. Eligibility Criteria

2.1.1. Study Inclusion Criteria

- Peer-reviewed studies of each level of evidence according to Oxford Classification. We included randomized clinical trials (RCT) and non-randomized controlled studies (NRCT) designs such as observational studies (OS), pre-post interventional studies (PPIS), and case-series studies (CS). We excluded case reports, technical notes, letters to editors, instructional courses, in vitro studies, cadaver investigation, systematic reviews, and meta-analyses.
- Studies including elderly patients (mean age > 65 years) suffering by CLBP (at least > 3 months).
- Clinical outcomes (disability and pain) of patients treated with PA (cardiovascular or aerobic) or exercise programs that included loaded (against gravity or resistance) as a component. To define a study as eligible, it had to include at least one pain assessment or one disability assessment. The disability outcome needed to be evaluated by one or more of the following scales: 36-Item Short Form Health Survey (SF-36) Version 1.0 and 2.0 (SF-36); Roland Morris Disability Questionnaire

(RMDQ); Oswestry Disability Index (ODI); and Back function (FFBH-R) [27]. The pain outcome had to be evaluated by one or more of the following scales: Numerical pain rating scale (NRS); Global Rating Change (GRC); Patient Pain Questionnaire (PPQ); and Visual rating scale (VRS).

- Only articles written in English and Italian languages were included.

2.1.2. Study Exclusion Criteria

- Studies with a mean age of patients < 65 years old;
- Studies in which PA was a part of a multidisciplinary program;
- Studies including participants who had physical problems that did not allow them to perform PA (diabetes untreated, muscle-skeletal problems, postural problems, neurological diseases, cardiovascular conditions).

2.2. Search Protocol

The following articles were screened from inception to March 2019: Medline, Scopus, CINAHL, EMBASE, and CENTRAL. For the search strategy we decided to use the following keywords: "low back pain" OR "chronic low back pain" AND "physical activity" OR "physical therapy" AND "elderly" OR "old aged" OR "older age" AND "Meziere" AND "Souhard" AND "global postural rehabilitation" "Feldenkrais" AND "McKenzie" AND "back school program" AND "Tai-Chi" AND "Pilates" AND "water therapy" OR "hydrotherapy" OR "balneotherapy" OR "hydrokinesis." We used the keywords isolated or combined. We searched for more studies among the reference lists of the selected papers and systematic reviews.

2.3. Study Selection

We accepted only English and Italian publications. The initial search of the article was conducted by two reviewers (D.S.S. and C.G). They used the protocol of search previously described to identify literature. In case of disagreements, the consensus of a third reviewer (R.F.) was asked. The researchers used the following research order. Titles were screened first, then abstracts and full papers. A paper was considered potentially relevant and its full text reviewed if, following discussion between the two independent reviewers, it could not be unequivocally excluded on the basis of its title and abstract. The full text of all papers not excluded on the basis of abstract or title was evaluated. The number of articles excluded or included were registered and reported in a PRISMA flowchart (Figure 1). For designing the PRISMA we followed the rules by Moher et al. [28].

2.4. Data Extraction

Data were extracted on: author, n of participants, year of study, content of intervention and control group, follow-up, outcomes (disability and pain), and mean age.

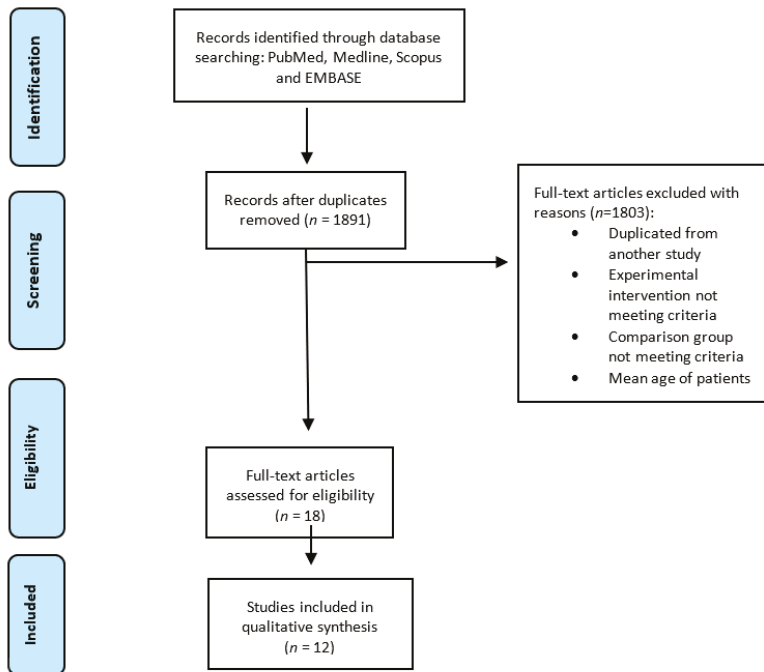


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.

2.5. Quality of Evidence

To estimate the potential bias that were most relevant for the study, we used the following tools: the Cochrane tool for assessing risk of bias in randomized trials (RoB 2 tool) [29] (Table 1) and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) [30] (Table 2). In order to avoid imprecisions, the elected papers were rated independently by two reviewers (E.A. and S.D.S.) and verified by a third (G.V.). We used the GRADE approach (Tables 3 and 4) to rate the overall quality of evidence. However, only six articles [31–36] showed full post-treatment data, therefore it was not possible to assess all the studies included using GRADE approach. The GRADE approach classifies the quality of evidence for each outcome grading the following domains: study design, risk of bias, inconsistency, indirectness, imprecision, publication bias, magnitude of the effect (not assessed in this study), dose-response gradient (not assessed in this study), and influence of all plausible residual confounding (not assessed in this study). The quality of evidence was then classified as follow:

- High Quality of Evidence: among 75% of articles included are considered with low risk bias. Further researches are useful to change either the estimate or confidence in results.
- Moderate Quality of Evidence: one of the GRADE domains is not met. Further studies are required to improve the quality of the study and the evidence.
- Low Quality of Evidence: two of the GRADE domains are not met. Further research is very important.
- Very Low Quality of Evidence: three of the GRADE domains are not met. The results of the study are very uncertain. In the case of studies with a sample size inferior to 300 subjects the quality of the study is considered very low if there was also a high risk of bias (assessed with different tools. In our study we used Rob2 and ROBINS-I).

Table 1. Cochrane tool for assessing risk of bias in randomized trials (RoB 2 tool).

Unique ID	Randomization process	Deviations From Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Vincent et al. 2014	?	+	+	+	?	?
Vincent et al. 2014 II study	+	+	?	+	+	?
Tsatsako et al. 2016	+	+	+	-	?	-
Costantino et al. 2014	?	+	+	-	?	?
Ferrel et al. 1996	-	+	+	+	?	-
Teut et al. 2016	+	+	+	+	+	+
Holmes et al. 1996	+	+	-	-	?	-




 : low risk;
  : some concern;
  : high risk.

Table 2. Risk of bias in non-randomized studies of interventions (ROBINS-I).

Unique ID	D1	D2	D3	D4	D5	D6	D7	Overall
Iversen et al.	X	-	+	-	X	-	-	X
Beissner et al.	!	X	-	-	X	X	X	!
Khalil et al.	!	X	+	-	-	+	-	-
Mailloux et al.	X	-	-	+	-	-	-	-
Hicks et al.	-	-	+	+	-	-	-	-





 : Critical;
  : Serious;
  : Moderate;
  : Low.

Table 3. GRADE evidence profile.

No of Studies	Study Design	Certainty Assessment					No of Patients	Effect Absolute (95% C.I.)	Certainty	Comments
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations				
Disability RCTs (assessed with: ODI; Scale from: 0% to 100%)										
2 [33,35]	randomized trials	not serious	serious	not serious	serious	none	52	46	MD 1.24% lower (1.94 lower to 0.54 lower), ($p = 0.0005^*$)	PA group shows a lower ODI mean value after treatment. It represents a possible positive influence of PA in improving disability
Disability RCTs (assessed with: SF-36; Scale from: 0 to 100)										
2 [31,32]	randomised trials	not serious	serious	not serious	serious	none	77	67	MD 2.88 point higher (-3.30 lower to 9.6 higher), ($p = 0.36$)	PA group shows a higher SF-36 mean value after treatment. It represents a possible positive influence of PA in improving disability
Pain RCT (assessed with: NRS; Scale from: 0 to 10)										
1 [36]	randomized trials	not serious	not serious	not serious	serious	none	35	17	MD 1.73 points lower (3.11 lower to 0.35 lower), ($p = 0.01^*$)	PA group shows a lower mean NRS after treatment. It represents a possible positive influence of PA in improving pain
Pain NRCT (assessed with: Global Rating Change; Scale from: 1 to 10)										
1 [34]	observational studies	serious	not serious	not serious	serious	none	238	154	MD 1 points lower (1.53 lower to 0.47 lower), ($p < 0.001^*$)	PA group shows a lower mean pain value after treatment. It represents a possible positive influence of PA in improving pain

C.I.: confidence interval; MD: mean difference; *: statistically significant; NRCT: non-randomized controlled trials; RCT: randomized controlled trials; PA: physical activity; SF-36: 36-Item Short Form Health Survey; ODI: Oswestry Disability Index; NRS: Numerical pain rating scale.

Table 4. GRADE summary of findings table.

Outcomes	Anticipated Absolute Effects * (95% C.I.)	№ of Participants (Studies)	Certainty of the Evidence (GRADE)
	Risk with PA		
Disability RCTs assessed with: ODI Scale from: 0% to 100%	MD 1.24% lower (1.94 lower to 0.54 lower), ($p = 0.0005 *$)	98 (2 RCTs) [33,35]	⊕⊕○○ LOW
Disability RCTs assessed with: SF-36 Scale from: 0 to 100	MD 2.88 point higher (−3.30 lower to 9.6 higher), ($p = 0.36$)	144 (2 RCTs) [31,32]	⊕⊕○○ LOW
Pain RCT assessed with: NRS Scale from: 0 to 10	MD 1.73 points lower (3.11 lower to 0.35 lower), ($p = 0.01*$)	52 (1 RCT) [36]	⊕⊕⊕○ MODERATE
Pain NRCT assessed with: Global Rating Change Scale from: 1 to 10	MD 1 points lower (1.53 lower to 0.47 lower), ($p < 0.001 *$)	392 (1 observational study) [34]	⊕⊕○○ LOW

MD: mean difference, *: statically significant; C.I.: confidence interval.

The outcomes assessed were improvement in pain and disability, both evaluated at the end of the treatment. Follow-up were different and ranged from 1 month to 48 months. Furthermore, the outcomes were subgrouped into RCTs, NRCTs, and other studies (pre-post intervention and case series).

3. Results

3.1. Study Selection

We created a flow-chart diagram according to the PRISMA protocol that shows the selection process of the studies (Figure 1). We found a total of 2173 studies (no additional studies were found in gray literature). We obtained 1891 studies when the duplicates were removed. Of the 1891 studies, 1709 articles were excluded from our study through the title screening. We assessed the abstracts of 182 articles and we excluded 94. Then, 88 full-text articles were screened. Out of these studies, 76 were excluded for the following reasons: mean age of patients < 65 years old ($n = 64$); experimental intervention not meeting the inclusion criteria ($n = 8$), and comparison group not meeting the inclusion criteria ($n = 4$). After this process, we included 12 articles in our study. No unpublished studies were retrieved.

3.2. Study Characteristics

A description of the characteristics of the studies that was considered eligible for this review is reported in Table 5. A total of 12 articles were selected for this systematic review. We included 7 RCT of I level of evidence (LOE), 3 NRCT (3 OS of II LOE), 1 PPS of III LOE, and 1 CS of IV LOE. Studies were published between 1992 [37] and 2016 [31].

Table 5. Characteristics of the included studies.

Study	Type of Study (LOE)	n. of Patients/Mean Age (y)	Exclusion	Inclusion	Type of Intervention	Control Group	Frequency	Outcome Summary	Outcome Measure/Difference Between Groups	Conclusions
Mailoux et al. [38] 2006	CS (IV)	126/76/48	Compression fracture within the last 6 months, and lack of cognitive or language skills necessary to complete paper-and-pencil measures.	CLBP	Stretching and endurance	No	6 weeks 2 session/week 2 hour/session	Disability Pain	ODI T0-T1 value Physical activity group: 28 (17 to 16 (13)) ($p = 0.01$) Control: 38 (17) to 25 (17) ($p = 0.01$)	The exercise behaviours of older adults with CLBP can increase after an exercise-oriented spine physical therapy.
Reisser et al. [39] 2012	OS (II)	59/75.5/72	Not reported	Patients >60 years old; ability to speak English or Spanish; LBP in the past three months, cognitively intact	Overall fitness: warmup, stretching, endurance exercises, walking, and a cool down	No	9 weeks 2 session/week	Disability	RMDQ T0-T1 values Physical activity group: 3.12 (0.72) to 7.83 (0.77), ($p < 0.001$)	The race/ethnicity could have a role in the improvement of CLBP with a conservative treatment
Iversen et al. [40] 2003	PPIS (III)	26/72/3	Pain with lumbar flexion; low back surgery in the last year; epidural steroid injection during the last 6 months; currently receiving physical therapy or participating in an exercise training program; other medical problems that limited their function more than LBP	Patients >65 years old; low back, buttock, and/or leg pain exacerbated by passive lumbar extension in standing; and symptoms that last for at least 6 months.	Indoor cycling	No	3 months 3 session/week	Disability	SF-36 T0-T1 Physical activity group: 7.2 ($p = 0.6$)	The bicycle program was safe and effective for improving functional status and well-being.
Costantino et al. [41] 2014	RCT (I)	56/73.46/3	Musculoskeletal disorders, cardiac diseases; fever or infectious disease; previous spinal surgery, trauma; previous physical therapies in the last three months	Patients >65 and <80 years old; Diagnosis of chronic non-specific low back pain; Chronic low back pain recurrence in the last three months.	Back school Program Hydrotherapy	Yes: Hydrotherapy	3 months 2 session/week 1 hour/session	Disability	RMDQ T0-T1 difference Back school: 3.26 ± 1.02, ($p < 0.001$); Hydrotherapy: 4.96 ± 0.71 ($p < 0.001$) SF-36 (Version 2.0) T0-T1 difference Back school: 13.30 ± 1.44 ($p < 0.001$); Hydrotherapy: 14.19 ± 1.98 ($p < 0.001$)	Back School program and Hydrotherapy could be valid treatment options in the rehabilitation of non-specific CLBP in older people.

Table 5. Contd.

Study	Type of Study (LOE)	n. of Patients/Mean Age (y)	Exclusion	Inclusion	Type of Intervention	Control Group	Frequency	Outcome Summary	Outcome Measure/Difference Between Groups	Conclusions
Ferral et al. [32] 1997	RCT (I)	33/73/1.5	Unstable cardiovascular or pulmonary diseases, inflammatory arthritis or nerve root compression; psychiatric disease, or alcohol abuse	Age >65 years CLBP, use of analgesic medication, ability to walk independently and able to understand and read English.	Three groups: Group 1: low intensity walking; Group 2: pain education program; Group 3: usual care	Yes: Education programme (one 90-minute session + weekly telephone reinforcement)	6 weeks 4 session/week 1 hour/session	Pain Disability	SF-36 (Version 1.0) TO-T1 difference Intervention: 38.5 (27.7), Control: 43 (16.7), PQ TO-T1 difference Intervention: 28.9 (18.5), Control: 57.8 (24.9), ($p < 0.001$)	Patient education and fitness walking can improve overall pain management and related functional limitations
Hicks et al. [34] 2012	OS (II)	392/66.8/12	Unstable-angina, hypertension, pulmonary disease, dementia, aphasia, back pain attributable to organic causes, back, presence of 2 or more of the following sign: lower-extremity strength, sensation, or reflexes	LBP > 4 months, capability to rise from a chair and walk, capability to travel to the exercise facility, and limited participation in physical activity at the initiation of the exercise program	Strengthening: abdominal strengthening, thoracolumbar, and scapula retraction in lying or standing position or sitting Stretching: hamstring and calf Endurance: 5–10 minutes walking	No	12 months 2 session/week 1 hour/session: 20–30 steps	Pain Adherence to exercise Performance	GRC TO-T1 difference Physical activity group: 4.6 (2.5) Control: 4.9 (2.7) ($p = 0.246$)	Patients were able to safely participate in exercise program and back pain improved 12 months later.
Holmes et al. [42] 1996	RCT (I)	38/68.3/3	Not reported	CLBP	Flexion and extension cycles of isotonic resistance exercises	Yes: No exercises	4 weeks 2 session/week	Pain	VRS TO-T1 values Physical activity group: from 5.3 to 2.1 ($p < 0.05$) Control: data not reported ($p > 0.05$)	In many patients lumbar exercises and resistance exercises could improve CLBP
Khalil et al. [37] 1992	OS (II)	59/68/1	Not reported	In the active restoration program: Low back pain and a diagnosis of myofascial pain syndrome. In the passive restoration program: weakness of quadriceps and/or tibialis anterior.	Mixed isotonic and isokinetic progressive resistive exercise of muscles	No control group The passive approach was based on the use of functional electric stimulation (FES) as an adjunct treatment to strengthen lower extremity muscles weakened by disuse	4 weeks 1 session/day	Pain	Pain level 1–10 TO-T1 values Physical activity group: 5.5 to 3.3 ($p < 0.01$) Control: data not reported	Physical activity can improve symptoms and functional ability of older people that suffer of older back pain. Moreover, FES could be a helpful device in the rehabilitation of weak muscles

Table 5. Contd.

Study	Type of Study (LOE)	n. of Patients/Mean Age (y)	Exclusion	Inclusion	Type of Intervention	Control Group	Frequency	Outcome Summary	Outcome Measure/Difference Between Groups	Conclusions
Teut et al. [31] 2016	RCT (I)	176/73	Acute neurological symptoms within the last 3 months, severe organic or psychiatric disease, metastatic bone disease	Adults ≥65 years old, chronic low back pain for at least 6 months	Yoga group: Vinyoga method Qijong group: "Dantian" and Nei Yang Gong exercises from the Taijiao System Liu Ya Fei	Yes: No: intervention group	Yoga group: 3 months 24 classes 45 minutes/class Qijong group: 3 months 12 classes 90 minutes/class	Disability	SF-36 TO-T1 value Yoga: 36.3 ± 8.7 to 59.47 (C.I. 54.73; 64.21) Qijong: 37.5 ± 7.8 to 61.01 (C.I. 55.88; 66.14) Control: 36.5 ± 9.3 to 61.17 (C.I. 56.32; 66.02), FFHR TO-T1 value Yoga: 68.7 ± 15.4 to 66.55 (C.I. 62.89; 70.21) Qijong: 70.4 ± 18.7 to 69.23 (C.I. 65.9)	High satisfaction of patients with the yoga and qigong classes, but participation in a 3- or 6-month period of yoga or qigong program did not improve chronic back pain, back function and quality of life.
Tsatsakos [33] et al. 2014	RCT (I)	80/67.71		Patients >60 years old, of both sexes and with pain in the lumbar region for a period over 12 weeks	10,000 steps/day performed on a treadmill and during the common life.	Yes: recommendation relaxation, and ergonomic	1 month 8000 steps/day	Disability	ODI TO-T1 value Physical activity group: 7.56 (3.22) to 8.06 (4.94) Control: 11.77 (5.27) to 10.00 (5.03), p = 0.46	Walking shows that it has no effect in the functional status of the elderly with CLBP.
Vincent et al. [36] 2014	RCT (I)	49/68.54		In men and women, BMI ≥30 kg/m ² , LBP for ≥6 months	Resistance exercise intervention (TOTRX) Lumbar extension intervention (LEXT)	Yes: No: intervention	TOTRX: 4 months, 3 session/week 15 exercise/session LEXT: 4 months, 3 session/week 2 sets of lumbar	Disability	ODI TO-T1 values TOTRX: 29.4 (11.2) to 18.0 (12.6) LEXT: 28.6 (15.2) to 22.6 (14.2) Control: 24.4 (12.1) to 22.9 (12.4), (p = 0.015) RMDQ	Resistance exercise show improvement in patients walking endurance. Lumbar extension strength in obese older adults with CLBP.
Vincent et al. [36] 2014	RCT (I)	49/68.54	Wheelchair bound, ability to participate in resistance exercise, acute back pain back surgery within the previous two years	CLBP > 6 months and abdominal obesity and free of abnormal cardiovascular responses during electrocardiogram (ECG) screening tests	TOTRX: 4 months, 3 session/week 15 sets/exercise/session LEXT: 4 months, 3 session/week 2 sets of lumbar reps/exercise/session	Yes: Behavioural advice: strengthening exercise and nutritional choices		Pain	NRS T1 value TOTRX: 4.3 (1.8) to 2.0 (1.7) LEXT: 5.0 (1.8) to 3.7 (2.6) Control: 5.2 (2.4) to 4.6 (2.4), (p < 0.006)	Total body resistance exercise (including lumbar extension exercise) was more effective than lumbar extension exercise alone in reducing self-reported disability scores due to back pain

CLBP: chronic low back pain, LBPL low back pain; CS: case-series; LOE: level of evidence; LEXT: lumbar extension intervention; TOTRX: resistance exercise intervention; ODI: Oswestry disability index OS; observational studies; NRS: numerical pain rating scale (NRS); PPS: pre-post interventional study; PPG: patient pain questionnaire; RCT: randomized clinical trial, RMDQ: Roland Morris Disability Questionnaire; VRS: Visual rating scale; SF-36: 36-item short form health survey; FES: functional electric stimulation; TO: baseline values; T1: last follow up values; C.I.: confidence interval; numbers reported in brackets refer to standard deviations.

Based on the data of the included studies, a total of 1581 patients were treated for CLBP. The mean age of patients at the time of treatment was 71.88 ± 3.01 and ranged between 67.5 [36] and 76.0 [42].

The outcome measures used in these studies included: (3 studies) 36-Item Short Form Health Survey (SF-36) Version 2.0 (SF-36); (3 studies) Roland Morris Disability Questionnaire (RMDQ); (3 studies) Oswestry Disability Index (ODI); (2 studies) Numerical pain rating scale (NRS); (1 study) SF-36 Version 1.0; (1 study) Patient Pain Questionnaire (PPQ); (1 study) Global Rating Change (GCR); (1 study) Visual rating scale (VRS); and (1 study) Back function (FFBH-R) [27].

The studies cited in this review show high heterogeneity in terms of study design, interventions, and outcome variables. The results are presented descriptively, focusing on disability and pain and further issues of potential interest. In general, post-treatment data showed a moderate range of improvement for disability and pain. Otherwise, these results need to be evaluated carefully due to the high risk of bias and the high heterogeneity of the studies included.

3.3. Methodological Quality

The Rob2 tool for RCT and ROBINS-I tool for NRCT, pre-post intervention and case-series were used to assess the methodological quality of each study. For RCT we found three studies with an overall risk identified as “some concerns,” 3 as “high risk,” and 1 as “low risk”. Concerning the NRCT we found 1 study with an overall risk of bias identified as “critical” [38] and 2 studies as “moderate” [34,37]. We assessed the pre-post intervention study with an overall risk of bias identified as “serious” [41]; instead the case series was identified as “moderate” [42].

The quality of evidence of the studies included in GRADE ranges from low to moderate. All the studies, except one [34], have a small sample ($n < 300$). Methodological quality assessments of each study are summarized in Tables 1 and 2. The quality of evidence of full data trials was performed using GRADE approach (Tables 3 and 4). The analysis of the data of the study was reported using the mean difference between studies. RevMan5 (version 5.3) was used to calculate the mean difference of the included studies. Because of the lack of post treatment results in some studies, we decided to perform a systematic review and not a meta-analysis. We report the outcomes of each study in Table 5.

3.4. Results of Individual Studies

The intervention methods are usually well described in all the included studies. High heterogeneity in the type of PA was reported in all the studies. We included all types of PA (walking [32,35], back school and hydrotherapy [39], isotonic resistance exercises [40] yoga and qijong [31], TOTXR [33] and LEXTR). The authors divided the description of intervention per outcome (pain and disability) in three subgroups (randomized controlled trials, non-randomized controlled trials, and other studies, including pre-post intervention and case series).

3.4.1. Randomized Controlled Trials (RCTs)

Seven RCTs were included. They were divided per outcome: 2 studies [36,40] examined the improvement in pain (measured by NRS and VRS); 5 studies [31–33,35,39] assessed the disability outcome (measured by ODI, RMDQ, PPQ, FRI, FFBH-R, and SF-36). Single studies were assessed for risk of bias using Rob2 tool. Two studies were classified as “high risk,” three as “some concerns,” and one as “low risk.” It was possible to include only 5 articles in GRADE analysis [31–33,35,36]. The overall quality of evidence in these studies ranges from “low” to “moderate” according to GRADE. The quantitative effect estimate was reported as mean difference between and within studies (when possible). This heterogeneity among studies and the low quality of evidence could lead to an overestimation of the results. The results of the outcome of the other studies are reported in Table 5.

Outcome: Pain

Two RCTs studies [36,40] presented data on pain at the end of the treatment. The authors used NRS and VRS to evaluate the improvements in pain. Follow-up was 3 months in the study carried

out by Holmes et al. [42] and 4 months in the study by Vincent et al. [36]. At the end of the treatment, they both reported a reduction of pain in the group treated by PA (isotonic resistance exercises in Holmes et al. [42] group and TOTXR and LEXTR in Vincent [36] group). The study by Holmes et al. was classified as “high risk,” and the risk of bias of the study by Vincent et al. was assessed as “some concern” using Rob2 tool. The study by Vincent et al. [36] was assessed as “moderate” quality using GRADE analysis. It was not possible to evaluate the overall quality of the other study according to GRADE [26] because of the lack of data. Otherwise, in both articles it was reported an improvement in pain evaluated by NRS and VRS. Vincent et al. [36] reported a better NRS in the intervention group compared to the control group at the end of the treatment (MD -1.73 , 95% C.I. -3.11 to -0.35 , $p = 0.01$). Holmes et al. [42] reported a difference from 5.3 to 2.1 points in VRS from the beginning to the end of the treatment (no full data were reported concerning to control group results). Otherwise, the authors reported an improvement in pain between the intervention and the control group, but this was not statistically significant ($p > 0.05$). The results of the outcome of the other studies are reported in Table 5.

Outcome: Disability

Five RCT studies [31–33,35,39] presented data on disability at the end of the treatment. The authors used ODI, RMDQ, SF-36, PPQ, FRI, and FFBH-R to assess the improvements in disability. Follow-up was heterogenous: 1 month for Tsatsakos et al. [35]; 1.5 months for Ferrel et al. [32]; 3 months for Teut et al. [31] and Costantino et al. [41]; and 4 months for Vincent et al. [33]. At the end of the treatment, all studies reported an overall improvement in disability. The PA program was different between studies (walking [32,35], back school and hydrotherapy [39], yoga and Qijong [31] and TOTXR [33]). In the study by Ferrel et al. [32] the control group was constituted by the hydrotherapy group and not by a no-intervention group as in the other studies. Also, in this study they reported an overall increase in disability in both groups. The studies by Tsatsakos et al. and Ferrel et al. were classified as “high risk,” Teut et al. as “low risk,” Costantino et al. and Vincent et al. as “some concern” using Rob2 tool. It was not possible to assess the quality of evidence of the study by Costantino et al. [41] because of the absence of a “no-intervention” control group. The overall quality of the other 4 studies [31–33,35] was evaluated as “low” according to GRADE [26]. In specific, the authors divided the studies into two subgroups: RCTs measured by ODI and RCTs measured by SF-36. We used only these scales since they were reported in all studies. We found a reduction of disability evaluated by ODI (MD -1.24 , 95% C.I. -1.94 to -0.54 ; $p = 0.0005$ *). Moreover, an improvement of SF-36 in patients treated by PA was reported (MD 2.88, 95% C.I. -3.30 to 9.06, $p = 0.36$). Costantino et al. [41] observed a highly significant statistical difference of SF-36 (13.30 ± 1.44 , $p < 0.001$ *), measured in both intervention groups (back school and hydrotherapy) at the end of the treatment. The results of outcome of the other studies are reported in Table 5.

3.4.2. Non-Randomized Controlled Trials (NRCT)

We included in our review three NRCT [34,37,38] studies. They were divided per outcome: 2 studies [34,37] examined the improvement in pain (measured by GRS and PPQ); 1 study [38] assessed the disability outcome (measured by RMDQ). The latter study did not have a control group. Single studies were assessed for risk of bias using ROBINS-I tool [30]. Two studies [34,37] were classified as “moderate” overall risk and one [38] as “critical.” Because of the lack of data, it was possible to assess the quality of evidence, according to GRADE, only of the study by Hicks et al. [34] classifying as “low.” The quantitative effect estimate of this study was reported as mean difference between groups. The high heterogeneity among studies and the low quality of evidence could lead to an overestimation of the results. The results of outcome of the other studies were reported in Table 5.

Outcome: Pain

Two NRCT studies [34,37] presented data on pain at the end of the treatment. The authors used GRS and PPS to evaluate improvements in pain. Follow-up was 1 month in the study by Khalil et

al. [37] and 12 months in the study by Hicks et al. [34]. At the end of the treatment they both reported a reduction of pain in the group treated by PA (strengthening and stretching programs [34] and isotonic and isokinetic progressive resistive exercise [37]). The overall quality of the study by Hicks et al. [34] was evaluated as “low” according to GRADE [26]. The study by Khalil et al. [37] was classified as “moderate” risk of bias using ROBINS-I tool. In specific, Hicks et al. [34] reported an improvement in pain after the treatment in the intervention group compared to controls measured by GRC (MD-1.00, 95% C.I. -1.53 to -0.47, $p = 0.006$ *). Khalil et al. [37] also reported a reduction of pain measured by pain scale (1–10) from 5.5 to 3.3 ($p < 0.01$ *), but no data concerning to control group were found.

Outcome: Disability

One NRCT study [38] presented data on disability at the end of the treatment. The authors used RMDQ to evaluate improvements in disability. Follow-up was 2 months. One important limitation in the study was the lack of a control group. However, at the end of the treatment the authors concluded by reporting an improvement in disability in the group treated by PA (stretching and resistance exercises [38]). The risk of bias of this study was evaluated using ROBINS-I and it was classified as “serious.” Beissner et al. [39] reported a reduction of disability measured by RMDQ scale in patients treated by PA (-5.29 points, $p < 0.001$ *).

3.4.3. Other Studies (Pre-Post Intervention and Case Series)

One pre-post intervention study [41] and one case series [42] presented data on disability at the end of the treatment. The authors used respectively SF-36 and ODI to evaluate improvements in disability. One important limitation of these studies was the lack of a control group. Because of the lack of a control group it was not possible to classify the evidence of these studies according to GRADE. Otherwise, the study by Mailloux et al. [38] was classified as “moderate” risk and Iversen et al. [40] as “serious” according to the ROBINS-I tool.

Outcome: Disability

Two studies [41,42] presented data on disability at the end of the treatment. They reported an improvement in disability in the groups treated by PA (cycling [41], stretching, resistance training, and endurance activities [42]). Follow-up was respectively 48 months in the study by Mailloux et al. [38] and 3 months in the study by Iversen et al. [40]. Iversen et al. [40] reported a non-statistically significant improvement in physical function measured by SF-36 of 7.2 points ($p = 0.6$). Mailloux et al. [38] reported a reduction of ODI from $28\% \pm 17$ to $16\% \pm 13$ ($p = 0.001$ *) in the intervention group after 48 months of follow-up. On the other hand, it was reported only a reduction of ODI from 38 ± 17 to 25 ± 17 ($p = 0.001$ *) in the control group.

4. Discussion

CLBP currently affects approximately one-fifth of the global population [43,44]. Cayea et al. reported that 36% of older adults aged 65 years or more are affected by at least one episode of this condition per year, of which 21% reported moderate or intense pain representing an important priority for the health system. In the literature, as confirmed by Paeck et al. [16], there is a lack of studies on CLBP in the elderly. In fact, most of the studies on CLBP treatment options are focused on the so-called “working age” and this calls into question the reliability of several treatment options in the older population, especially because in the older age we can often find several comorbidities that may limit the rehabilitation.

In our systematic review, we screened the recent literature (1992–2018) with the aim to assess the effectiveness of PA to improve disability and pain in the elderly population affected by non-specific CLBP comparing it to no treatment and other conservative treatments. Indeed, 12 studies were included at the end of the search process. Among these, only 5 RCTs with an overall quality of evidence that ranges from “low” to “moderate” and 1 NRCT of “low” quality could be assessed according to GRADE

approach. The quality of the other studies was evaluated by Rob2 for RCT and ROBINS-I for the other study types. The lack of data in some articles, and the poor literature among this topic could lead to low quality of evidence. Our research highlighted that older patients with CLBP treated with PA showed an overall pain and disability improvement in the majority of the studies. Otherwise, these conclusions need to be taken carefully, considering the high risk of bias, the low quality of evidence of the literature, and the languages limitations of this study (only English and Italian articles were included). Because of these limitations and the absence of high-quality literature, we decided to perform only a systematic review of the literature and not a meta-analysis.

However, the extreme variability of type, duration, intensity, and execution modality of the proposed PA, the different body district on which PA were focused on in each different program and the compliance of the patients, are important variables that make it impossible to recommend a specific protocol in the elderly population. This lack of standardization was also confirmed by Airaksinen et al. [18] that found a considerable variety of PA, such as stretching, aerobic exercises, or muscle reconditioning.

In this systematic review, we analyzed different PA protocols, based on walking [35], cycling [41], back school exercises [39], hydrotherapy [39], Yoga and Quigong [31], endurance, resistance, stretching and strengthening exercises [33,37]. Regarding the trained muscle groups, we found that most of the included studies were focused on abdominus muscles [40], iliopsoas, hamstring, gastrocnemius, quadriceps, hip flexors, abductor/adductor muscles of the hip and erector spinae muscles [37].

Regarding the 4 studies evaluating pain (2 RCTs and 2 NRCTs), they showed that both lumbar isotonic resistance exercise cycles and abdominal, thoracolumbar and upper limb isotonic and isokinetic strengthening exercises, improve pain in elderly patients with CLBP. In their RCT, Vincent et al. [32] also reported, at a 4-months follow-up, an improvement in walking speed and endurance. This finding confirms that the physical treatment of CLBP might be focused not only on the lumbar muscles but also on the lower limbs and thorax (exercises for breathing muscle districts [39]). Otherwise, one study [40] reported an improvement in pain, but not statistically significant if compared with the control group ($p > 0.05$).

The studies which assessed disability (5 RCTs, 1 NRCT, 1 pre-post intervention and 1 case series) confirmed that walking, back school exercise, hydrotherapy, yoga and Qijong, bicycle program, strengthening and stretching program, and combined PA and cognitive-behavioral program improve the functional performances of elderly people with CLBP. However, because of the high heterogeneity of the studies, we found a significant reduction of disability evaluated by ODI ($p = 0.0005^*$), but the improvement of SF-36 in patients treated by PA was not significant ($p = 0.36$). Moreover, we also found an improvement in patients treated by different types of PA such as back school and hydrotherapy [39] ($p < 0.001^*$) at the end of the treatment.

Other important concerns are compliance and motivation of the patient that may represent decisive parameters during CLBP treatment in the elderly. Beissner et al. [39] emphasized an interesting treatment option represented by the cognitive-behavioral therapy (CBT) in association with PA to reduce symptoms in patients with CLBP. This novel treatment is becoming increasingly important. In a recent systematic review, Vitoula et al. [45] highlighted that CBT was effective in patients with CLBP, especially in reducing pain perception and helping them to improve their functionality. Furthermore, the review showed that better outcomes can be achieved when treatments are personalized. This represents a remarkable issue. In fact, several studies included in our research [34,38,39] showed that patients that maintain a prolonged compliance to the rehabilitation protocols and were highly motivated had better outcomes in pain relief and function outcomes.

It is crucial to focus on the biological effects of PA [46,47]. One major limit to perform PA in old-aged patients is the sarcopenia, defined as a loss of muscle mass (lean body mass) with a reduction of muscle function [48]. This process represents a specific condition of normal energy balance in the elderly, with an increase in body fat percentage. Limb surgery postoperative period, disuse, endocrine diseases (such as diabetes type II), and uncontrolled nutrients intake lead to sarcopenia [49]. This

condition could lead to a frailty status, with a reduction of PA [50]. Landi et al. [51] conducted a review of the literature reporting that PA has an important role in the reduction of sarcopenia in old-aged people. PA could also increase irisin [52] and osteocalcin [53]. The former is a hormone-like myokine produced by skeletal muscle during PA [54]. Irisin can induce thermogenesis from brown adipocytes. This protein has also an effect in the control of bone mass, with positive effects on cortical mineral density. It is also demonstrated that irisin plays a crucial role in the reduction of sarcopenia in old people [55,56]. Osteocalcin is a bone-derived hormone-like protein. It could favor physiological functions increasing the bone formation [57], regulating the muscle decrease related to age [58], and reducing the risk of diabetes type II [4,59]. Chahla et al. [60] reported in their study that osteocalcin is higher in patients who perform regular PA, with an increase in bone mineralization, muscle function, and reduction of risk of diabetes type II.

Moreover, several studies [61–63] report that PA could also reduce the level of osteoporosis, resulting in a valid therapeutical approach for this disease in elderly people.

Limitations

The results of this study should be considered with caution, as there was a high heterogeneity in terms of follow-up, type of intervention, and standardization of physical protocols. In fact, the follow-up varies from a minimum of 1 month to a maximum of 48 months, as well as the number of patients (49 to 392). The small sample size and the high heterogeneity among trials as well as the absence of a control group in three studies [38,41,42], make the estimate of the effect of intervention extremely challenging. Moreover, the low quality of the studies (from “low” to “moderate”), and the high risk of bias of some studies included, decrease the power of our conclusions. Nevertheless, some studies reported an improvement of outcomes in patients treated by PA, even if their results were not statistically significant. These data could lead the authors to overestimate the results considered. Another important limitation of this systematic review is the decision of the authors to include only English and Italian articles. This limitation could lead to an exclusion of relevant studies related to this specific topic. Therefore, further high quality evidences that take into account the standardized methods and a similar cohort of patients are desirable. At the same time, this review should promote future investigations, also including other languages, to better understand which type of PA is preferred to treat older patients with CLBP and help our clinical practice.

5. Conclusions

In the available literature PA seems to have a trend of improvement in pain and disability in elderly patients with non-specific CLBP. However, because of the limited and low-quality literature it is not possible to state this positive effect as a definitive conclusion. In order to avoid the overestimated effectiveness of PA on CLBP from high risk of bias studies, new high-quality evidence is needed.

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Review

Return to Sport after Anatomic and Reverse Total Shoulder Arthroplasty in Elderly Patients: A Systematic Review and Meta-Analysis

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Abstract: The aim of this systematic review and meta-analysis was to evaluate the rate of return to sport in elderly patients who underwent anatomic (ATSA) and reverse (RTSA) total shoulder arthroplasty, to assess postoperative pain and functional outcomes and to give an overview of postoperative rehabilitation protocols. A systematic search in Pubmed-Medline, Cochrane Library, and Google Scholar was carried out to identify eligible randomized clinical trials, observational studies, or case series that evaluated the rate of return to sport after RTSA or ATSA. Six retrospective studies, five case series, and one prospective cohort study were included in this review. The overall rate of return to sport was 82% (95% CI 0.76–0.88, $p < 0.01$). Patients undergoing ATSA returned at a higher rate (90%) (95% CI 0.80–0.99, $p < 0.01$) compared to RTSA (77%) (95% CI 0.69–0.85, $p < 0.01$). Moreover, the results showed that patients returned to sport at the same or a higher level in 75% of cases. Swimming had the highest rate of return (84%), followed by fitness (77%), golf (77%), and tennis (69%). Thus, RTSA and ATSA are effective to guarantee a significant rate of return to sport in elderly patients. A slightly higher rate was found for the anatomic implant.

Keywords: shoulder; arthroplasty; replacement; return to sport; elderly; systematic review; meta-analysis

1. Introduction

Total shoulder arthroplasty (TSA) is the third most common replacement procedure after hip and knee arthroplasty and is considered the elective treatment for patients affected by advanced shoulder pathology with loss of function and severe pain [1]. Indeed, the main indications for shoulder replacement are primary and secondary glenohumeral osteoarthritis, osteonecrosis, and fractures of the proximal epiphysis of the humerus or its sequelae [1–5].

Three main different designs of shoulder prostheses allow surgeons to decide which is the best option for each specific case, trying also to meet patients' health needs [6]. The reverse shoulder arthroplasty (RTSA) has a specific design that determines the medialization of the rotation center, permitting the recruitment of a large part of the deltoid muscle [7]. Thus, even if the rotator cuff is damaged, the arc of movement is preserved [7]. Conversely, the biomechanics of the anatomic total shoulder arthroplasty (ATSA) is based on rotator cuff integrity. The third implant option includes

hemiarthroplasty (HHA) and humeral head resurfacing that differ from the above mentioned because they do not require glenoid replacement. Currently, these implants are more often indicated for the treatment of end-stage osteoarthritis as well as fractures of the humeral head in young patients [8]. As a consequence, the number of implanted HHAs has decreased in the last 15 years in favor of TSAs [1,9–11].

The constant increase of TSAs, in younger as well as older individuals, correlates with their good long-term outcomes and with the widening of surgical indications [1,2]. In this scenario, as life expectancy is increasing, older patients are also asking their surgeons for better outcomes in order to return to previous sports activities after surgery [3]. Return to sports activities at a preoperative level has widely been investigated for patients with hip and knee arthroplasties with satisfactory rates of return [4–6]. However, limited data exist regarding rates of return after TSA, even if this field is becoming of increasing interest. A recent multi-center international study, carried out by the American and European Society of Shoulder and Elbow Surgeons, stated that non-contact low-load activities with low risk of fall or collision were most frequently allowed by surgeons [7].

The TSA post-operative rehabilitation protocol plays an important role in active patients to achieve satisfactory post-operative clinical outcomes and range of motion (ROM) [8]. Despite the existence of a large number of studies about rehabilitation protocol after hip and knee replacement, there are still only a few papers focused on specific and standardized postoperative rehabilitation protocols for patients with TSA [9,10]. Current postoperative guidelines are usually based on the original protocol developed by Hughes and Neer [11]. This protocol contemplates different steps with a gradual mobilization of the arm, avoiding flexion and abduction movements until the fourth postoperative week, but it does not provide indications for rehabilitation finalized to the resumption of sports activities. Nevertheless, for these patients, a postoperative rehabilitation protocol with a specific exercise routine could be advisable [11–13].

The primary aim of this systematic review and meta-analysis is to evaluate the rate of return to sport in elderly patients after ATSA and RTSA. The secondary and tertiary endpoints focus on the assessment of postoperative pain and functional outcomes and to give an overview of current postoperative rehabilitation protocols.

2. Materials and Methods

The present systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [14]. In this review, we included randomized clinical trials, observational studies, and case series, which evaluated the return to sport of cohorts with an average age greater than 65 years who underwent RTSA and ATSA.

2.1. Eligibility Criteria

According to the Oxford Centre of Evidence-Based Medicine, peer-reviewed studies of I to IV levels of evidence were considered for inclusion. Case reports, studies on animals, biomechanical reports, technical notes, letters to editors, instructional courses, cadaver or in vitro investigations, systematic reviews and meta-analyses, or studies without an abstract were excluded. According to the definition of the elderly by the WHO, the search was focused on papers reporting on return to sports of cohorts, with an average age greater than 65 years who underwent RTSA and ATSA. Only studies with a minimum of 10 patients and a minimum of one-year follow-up were included. Moreover, only articles in Italian, English, Spanish, and French were considered.

2.2. Study Outcomes

The primary outcome of the analysis was to establish the rate of return to sport of elderly patients after ATSA and RTSA. Among the included papers, the secondary endpoint was to assess the postoperative pain and functional outcomes, taking into account the reported standardized clinical

scores. The tertiary endpoint of this systematic review was to give an overview of the proposed rehabilitation protocols.

2.3. Search Methods for Identification of Studies

A systematic literature search in Pubmed-Medline, the Cochrane Library and Google Scholar databases was carried out between September 2019 and April 2020. For Pubmed, the following search strategy was used: (((“Shoulder Joint”[Mesh] OR (“shoulder”[All Fields] AND “joint”[All Fields]) AND (“Arthroplasty”[Mesh] OR (“Arthroplasty”[All Fields]) OR (“Replacement”[All Fields])) AND (“Sports”[Mesh] OR (“return to sport” [All Fields] OR (“return” [All Fields] AND (“sport” [All Fields])) AND “Aged”[Mesh])). No time interval was set for publication date. Two independent reviewers (M.C. and C.D.A.) conducted the electronic search identifying the potentially relevant studies. Firstly, the retrieved articles were screened by title and, if relevant, by reading the abstract. After the exclusion of non-eligible studies, the full-text of the remaining articles was evaluated for eligibility. To minimize the risk of bias, the authors reviewed and discussed all the selected articles, the references, as well as the articles excluded from the study. If any disagreement between the reviewers was found, the senior investigator (R.P.) made the final decision. At the end of the process, further potentially missed studies were manually searched for among the reference lists of the included papers and the relevant systematic reviews.

2.4. Data Collection

All reviewers discussed the relevant items for data extraction before starting the process in order to avoid data omission. Data were independently extracted by two reviewers (M.C. and C.D.A.) and divergences were discussed with the third reviewer (R.P.) if necessary. All data related to primary, secondary and tertiary outcomes were summarized in standardized tables. Specifically, the following variables were recorded: authors, year of publication, type of study, level of evidence, number of participants, mean age, dominant or not-dominant limb, surgical approach, mean follow-up, complications, patients returned to sport and type of activity, secondary outcome measures, and rehabilitative protocols. Among the outcomes, we analyzed functional outcomes and severity of pain.

2.5. Risk of Bias Assessment

The quality of the included studies was independently evaluated by two reviewers (C.D.A. and M.C.) using the Methodological Index for Non-randomized Studies (MINORS) score [15]. The following domains were assessed: a clearly stated purpose, inclusion of consecutive subjects, prospective data collection, endpoints appropriate to the purpose of the study, unbiased assessment of the study endpoints, follow-up period appropriate for the study, loss to follow-up of less than 5%, prospective calculation of the study size, adequate control group, contemporary group, baseline group equivalence, and adequate statistical analysis. The last four items are specific to comparative studies. Each item was scored from 0 to 2 points, with a global ideal score of 16 points for non-comparative studies and 24 points for comparative studies.

2.6. Statistical Analysis

Meta-analysis was performed to determine the overall proportion of subjects returning to sport and the functional and pain level after shoulder arthroplasty across all the retrieved studies. Raw, i.e., untransformed, proportions and means were used to report the pooled proportions and means that were obtained with the inverse variance method. Heterogeneity was evaluated using Q statistic, expressed as the p value for the χ^2 test under the null hypothesis that the between-study variance (τ^2) equals 0, and I^2 test. All the conducted meta-analyses evidenced the presence of significant heterogeneity, defined as a $I^2 > 55\%$ and a Q statistic p value below 0.05. Accordingly, random effect models were applied. Finally, the likelihood of publication bias was estimated with a visual inspection

of the funnel plot. All analyses were carried out using metaphor and meta-packages in R 3.6.1 software for Mac (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study Selection

The initial database searches identified 235 potentially eligible papers. After reviewing title and abstract, 217 papers were excluded and 18 were selected for full-text evaluation. Out of these, eight papers were excluded for the following reasons: mean age of the cohort < 65 years ($n = 1$), German language ($n = 1$), return to sport not clearly stated ($n = 4$), and insufficient outcomes data ($n = 2$). One paper was added from hand search. At the end of the selection process, 11 studies were included in this systematic review and 11 papers were included in the meta-analysis [16–25]. The search process is summarized in the PRISMA flowchart (Figure 1) [14].

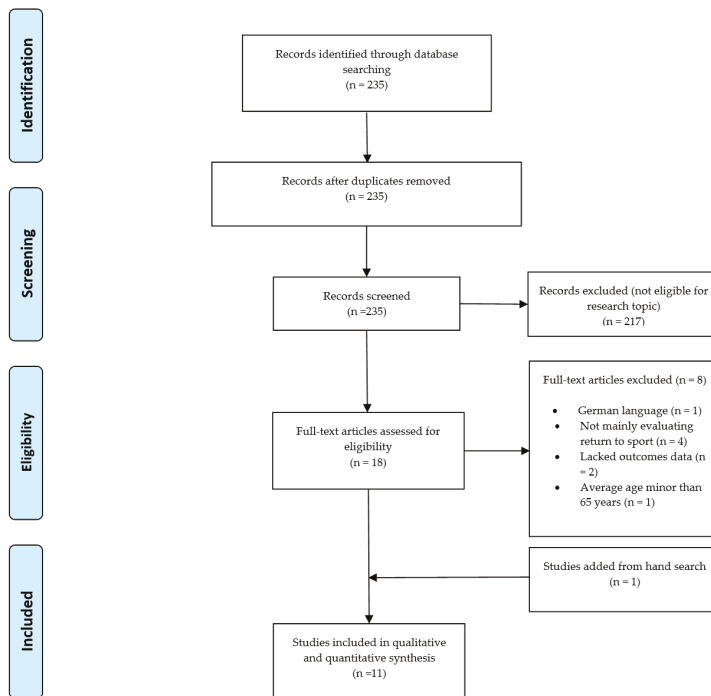


Figure 1. PRISMA flow-chart of included studies.

3.2. Study Characteristics and Demographic Details

Of the included studies, one was a single-center prospective cohort study (PCS) of level of evidence (LOE) III [19], four were retrospective studies (RS) of LOE III [18,20,23,25], one was a retrospective study of LOE IV [26], and five were case series of LOE IV [16,17,21,22,24]. All studies were published between 2010 [21] and 2018 [26]. The 11 included studies reported on 1254 shoulder arthroplasties in 1238 patients. Within the included studies, the number of subjects varied from 35 [24] to 276 [26]. The mean age of the cohorts was 72.5 years. The mean duration of follow-up was 3.7 years, ranging from 2.4 [26] to 6.2 years [17]. Four out of the 11 studies had a mean follow-up longer than four years [16,17,19,23]. The indications for surgery were several: rotator cuff arthropathy

(522 patients), primary osteoarthritis (270 patients), fracture sequelae (37 patients), and rheumatoid arthritis (15 patients). Pre-operative diagnosis was not specified for 367 patients [19,22,23,26].

In total, 375 ATSA and 750 RTSA were implanted. The side of surgery was specified in 9 studies [16–23,25]. The dominant shoulder was involved in 544 patients, while the non-dominant shoulder was treated in 288 patients. Bilateral shoulder arthroplasty was performed in 17 patients [17,24]. The most frequent indication for ATSA was primary osteoarthritis without cuff dysfunction [17,19,21,24]. Conversely, RTSA was performed in patients affected by primary osteoarthritis [16,20], cuff tear arthropathy [16,18,20,23,25], proximal humeral fractures [18,20,23], rheumatoid arthritis [18,20], and shoulder tumors [23]. Two studies did not specify surgical indications [22,26]. The main characteristics of the included papers are summarized in Table 1.

Table 1. Study characteristics, demographic details and Methodological Index for Non-randomized Studies (MINORS) score.

Authors	Year of Publication	Study Design	LOE	N° of Shoulders (N° of Patients)	Dominant/Not Dominant	Mean Age (Years)	Type of Implant	Mean Follow-Up (Years)	MINORS Score
Bulhoff et al. [17]	2015	CS	IV	170 (154)	103/51	72	ATSA	6.2	7/16
Bulhoff et al. [16]	2016	CS	IV	38 (38)	29/9	Group A: 76.2; Group B: 78.4	RTSA	4.8	14/24
Liu et al. [18]	2016	RS	III	102 (102)	58/44	72.3	RTSA	2.6	14/24
Kolling et al. [25]	2017	RS	III	271 (271)	203/68	77.1	RTSA	2.9	7/16
Schumann et al. [21]	2010	CS	IV	100 (100)	60/40	66.2	ATSA	2.8	8/16
Garcia et al. [19]	2016	PS	III	40 (40)	26/14	66.3	ATSA	5.1	9/16
Papaliodis et al. [24]	2015	CS	IV	36 (35)	NR	67.2	ATSA	3.2	8/16
Simovitch et al. [22]	2015	CS	IV	67 (67)	NR	73	RTSA	3.6	10/16
Barnes et al. [23]	2015	RS	III	78 (78)	48/30	75.3	RTSA	4.8	11/16
Garcia et al. [20]	2015	RS	III	76 (76)	46/30	74.8	RTSA	2.6	16/24
Kurowicki et al. [26]	2018	RS	IV	276 (276)	NR	RTSA: 75 ATSA: 69	RTSA ATSA	2.4	14/24

ATSA: anatomic shoulder arthroplasty; RTSA: reverse total shoulder arthroplasty; CS: case series; RS: retrospective study; PS: prospective study; LOE: level of evidence; NR: not reported. Group A: patients who practiced sports within the last 5 years prior to shoulder replacement surgery; Group B: patients that have never participated in sports activities.

3.3. Methodological Evaluation

The MINORS score ranged from 7 [17,25] to 11 [23] for non-comparative studies and from 14 [16,18] to 16 [20,26] for the comparative ones (Table 1). The mean value was 8.5 for non-comparative studies and 14.5 for comparative studies. All papers resulted at high risk of bias.

3.4. Return to Sport

The overall rate of return to sport for elderly patients was 82% (95% CI 0.76–0.88, $p < 0.01$) (Figure 2). Patients undergoing ATSA returned at a higher rate (90%) (95% CI 0.80–0.99, $p < 0.01$) compared to RTSA (77%) (95% CI 0.69–0.85, $p < 0.01$) (Figure 2). The time to resume sports was reported in five studies [18–21,24] with a mean period of seven months ranging from 5.3 [18,20] to 11 months [15,21]. The results [16–20,25] showed that patients returned to sports activities at the same or a higher level in 75% of cases (95% CI 0.61–0.89, $p < 0.01$) (Figure 3). Six out of 11 studies [16–20,25] (54.5%) reported sport-specific rates of return. When combined by meta-analysis according to a random-effects model, swimming had the highest rate of return (84%), followed by fitness (77%), golf (77%), and tennis (69%) (Figures 4–7). Regarding publication bias, the funnel chart was asymmetric, suggesting the presence of bias, particularly in smaller studies (Figure 8). The details of return to sport are reported in Table 2.

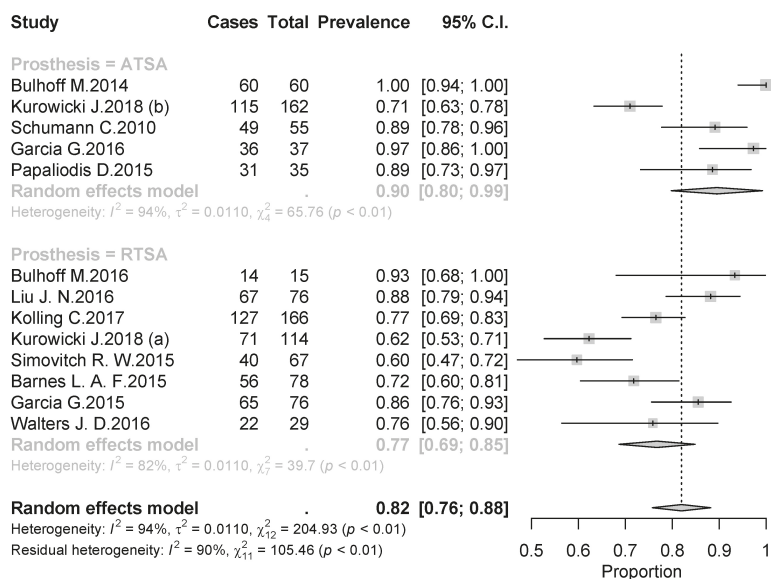


Figure 2. Forest plot chart of the combined rate of return to sports by meta-analysis with 95% confidence interval. ATSA, anatomic total shoulder arthroplasty; RTSA, reverse total shoulder arthroplasty.

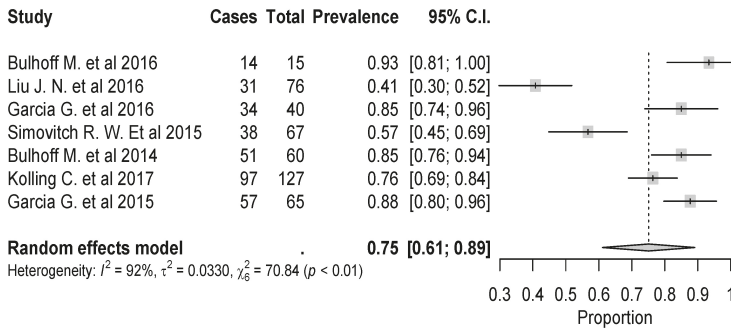


Figure 3. Forest plot chart of the rate of return to sports at the same or a higher level of play as before shoulder arthroplasty with 95% confidence interval.

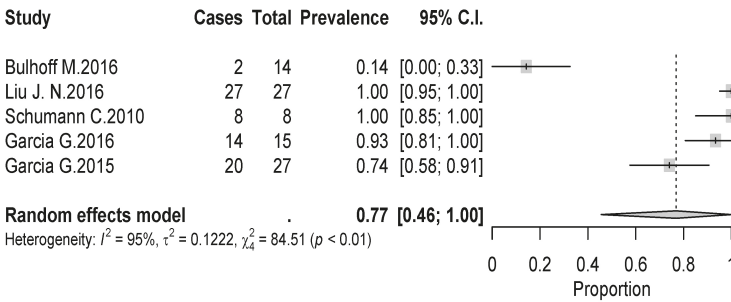


Figure 4. Forest plot chart of the rate of return to fitness after shoulder arthroplasty with 95% confidence interval.

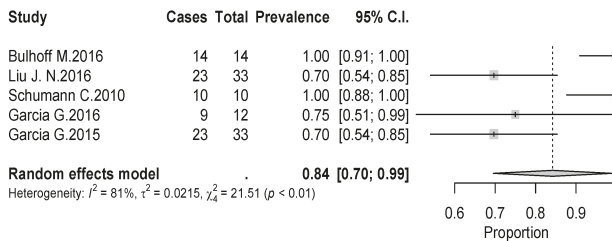


Figure 5. Forest plot chart of the rate of return to swimming after shoulder arthroplasty with 95% confidence interval.

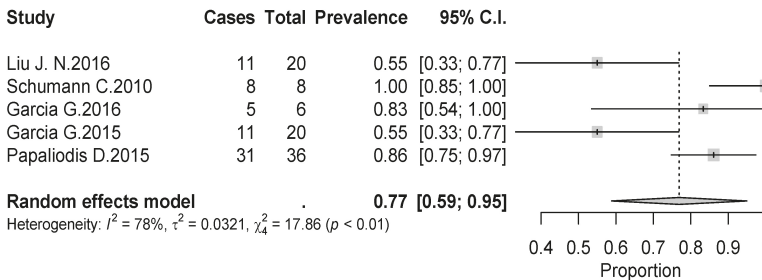


Figure 6. Forest plot chart of the rate of return to golf after shoulder arthroplasty with 95% confidence interval.

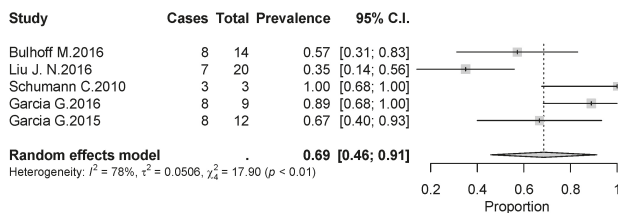


Figure 7. Forest plot chart of the rate of return to golf after shoulder arthroplasty with 95% confidence interval.

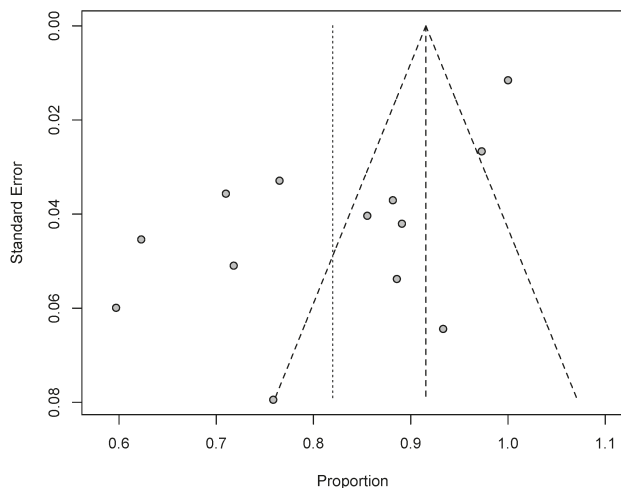


Figure 8. Funnel plot chart evaluating publication bias.

Table 2. Return to sport.

Study	Sports	Number of Patient Practicing Sport (%)	Number of Evaluated Patients	Rate of Return to Sport for Single Sport (%)	Overall Rate of Return to Sport (%)
Schumann et al. [21]	Swimming	10 (20.4%)			
	Golf	8 (16.3%)			
	Cycling	8 (16.3%)	55	NR	49 (89%)
	Fitness	8 (16.3%)			
	Other	21 (30.7%)			
Papaliodis et al. [24]	Golf	35 (100%)	35	NR	31 (88.57%)
	Fitness	27	76 (some patients practiced more than 1 sport)	22 (81.5%)	
Garcia et al., 2015 [20]	Swimming	33		22 (66.7%)	65 (85.5%)
	Golf	20		10 (50%)	
	Cycling	10		5 (50%)	
Bulhoff et al., 2015 [17]	Swimming			60 (57%)	
	Fitness including lower limb			42 (27%)	
	Skating			31 (30%)	
	Gardening			29 (28%)	
	Bowling/skittles	60 (57%)	105	18 (17%)	60 (100%)
	Tennis			15 (14%)	
	Handball			6 (4%)	
	Athletics			4 (3%)	
	Volleyball			3 (2%)	
	Golf			2 (1%)	
Other			26 (25%)		

Table 2. Cont.

Study	Sports	Number of Patient Practicing Sport (%)	Number of Evaluated Patients	Rate of Return to Sport for Single Sport (%)	Overall Rate of Return to Sport (%)
Bulhoff et al., 2016 [16]	Swimming			14 (100%)	
	Fitness including lower limb			8 (57%)	
	Skating	15 (71%)	22	7 (50%)	14 (93%)
	Gardening			8 (57%)	
	Bowling			7 (50%)	
	Tennis			8 (57%)	
	Handball			2 (14%)	
Kolling et al. [25]	Calisthenics			28 (17%)	
	Hiking			28 (17%)	
	Swimming	166	305	26 (16%)	127 (77%)
	Alpine skiing			13 (8%)	
	Tennis			12 (7%)	
	Others			58 (35%)	
	Single tennis	12 (12.2%)		4 (33%)	
	Double tennis	18 (18.3%)		3 (16.6%)	
	Baseball	1 (1.02%)		1 (100%)	
	Swimming	33 (33.66%)		23 (70%)	
Liu et al. [18]	Fitness	27 (27.54%)	102	27 (100%)	87 (85.9%)
	Golf	20 (20.4%)		11 (55%)	
	Cycling	12 (12.2%)		8 (67%)	
	Fishing	4 (4.8%)		1 (25%)	
	Rowing	1 (1.02%)		1 (100%)	
	Running	7 (7.14%)		5 (71.4%)	
	Skating	7 (7.14%)		2 (29%)	
	Dancing	2 (2.04%)		1 (50%)	
	Horseback riding	2 (2.04%)		1 (50%)	
	Basketball	1 (1.02%)		1 (100%)	

Table 2. Cont.

Study	Sports	Number of Patient Practicing Sport (%)	Number of Evaluated Patients	Rate of Return to Sport for Single Sport (%)	Overall Rate of Return to Sport (%)
Simovitch et al. [22]	Golf			50 (75%)	
	Swimming			19 (29%)	
	Water aerobics			16 (24%)	
	Deep sea fishing			14 (21%)	
	Firearm sports	67 (26%)	255	14 (21%)	64 (95%)
	Weight lifting			12 (18%)	
	Softball			7 (11%)	
	Tennis			7 (11%)	
	Table tennis			5 (7%)	
	Scuba diving			5 (7%)	
	Racquetball			3 (5%)	
	Surfing			1 (2%)	
Water skiing			1 (2%)		
Garcia 2016 et al. [19]	Golf	6 (8.3%)		5 (83.3%)	
	Swimming	12 (16%)		9 (75%)	
	Baseball	1 (1.4%)		1 (100%)	
	Basketball	1 (1.4%)	72	1 (100%)	65 (90.27%)
	Nature sports	7 (9.7%)		7 (100%)	
	Fitness	15 (21%)		14 (93%)	
	Single tennis	5 (7%)		4 (80%)	
	Running	14 (19.4%)		13 (92.9%)	
	Cycling	5 (7%)		5 (100%)	
	Softball	2 (2.7%)		2 (100%)	
	Double tennis	4 (5.5%)		4 (100%)	

Table 2. Contd.

Study	Sports	Number of Patient Practicing Sport (%)	Number of Evaluated Patients	Rate of Return to Sport for Single Sport (%)	Overall Rate of Return to Sport (%)
Barnes et al. [23]	High intensity activities (hunting, golf, skiing...)	NR	78	18 (23.1%)	100%
	Moderate intensity activities (swimming, bowling...)	NR		38 (48.7%)	
	Low intensity activities (riding bike, walking, dancing...)	NR		22 (28.2%)	
Kirowicki et al. [26]	Golf	RTSA: 16 (22%) ATSA: 31 (27%)	RTSA: 71 ATSA: 115	NR	RTSA 71/114 (62%); ATSA 115/162 (70%)
	Swimming	RTSA: 13 (18%) ATSA: 19 (16%)			
	Walking	RTSA: 16 (22%) ATSA: 18 (15%)			
	Gym exercises	RTSA: 8 (11%) ATSA: 24 (20%)			
	Racquet sport	RTSA: 4 (5%) ATSA: 13 (11%)			
	Group fitness	RTSA: 5 (7%) ATSA: 10 (8%)			
	Fishing and target shooting	RTSA: 5 (7%) ATSA: 4 (3%)			
	Adventure sport	RTSA: 1 (1%) ATSA: 9 (8%)			

NR: not reported.

3.5. Clinical Outcome Data

Outcome measures reported in the included studies are summarized in Table 3. The most frequently reported score was the American Shoulder and Elbow Surgeons (ASES) score, used in 6 (54%) of 11 studies [18–20,22,23,26], and the visual analog scale for pain (VAS) used in 4 (36%) studies [18–20,22] with an average of 76.23 (95% CI 0.81–0.90, $p < 0.01$) and 0.8 (95% CI 0.81–0.90, $p < 0.01$) points respectively (Figures 9 and 10). Constant score was used in two studies [21,22] and the evaluation of range of motion (ROM) was used in two studies [22,23].

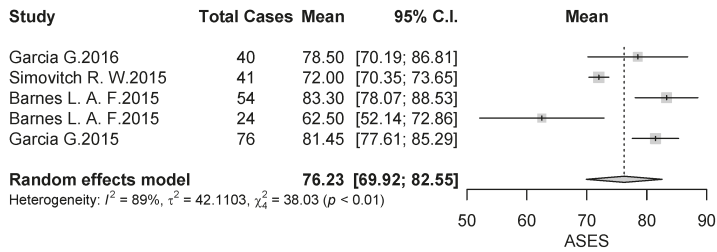


Figure 9. Forest plot chart of ASES score.

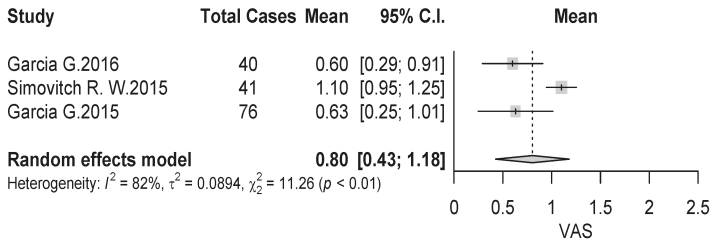


Figure 10. Forest plot chart of VAS score.

Table 3. Clinical outcome data of the included studies.

Authors	Implant	Outcomes		Complication (Number)	Main Conclusion
		Preoperative	Postoperative		
Bulhoff et al. [17]	ATSA	NR	NR	NR	- Patients with active sports participation before TSA are successfully able to return to sports activities after surgery. - Patients who are not participating in sports just before surgery are unlikely to resume sports after surgery.
Bulhoff et al. [16]	RTSA	NR		aseptic loosening of glenoid component (1), dislocation (2)	Patients with glenohumeral osteoarthritis and rotator cuff disease being active prior to RSA surgery are able to successfully return to their level of sports participation afterwards.
Liu et al. [18]	RTSA	ASES SCORE (overall mean change)		None	Despite traditional sport restrictions placed on RTSA, patients undergoing RTSA can return to sports at rates higher than those undergoing HHA, with fewer postoperative complaints.
		+39			
		VAS (overall mean reduction)			
			-5.64		
Kolling et al. [25]	RTSA	NR	NR	NR	- Most patients carried out their main sports activity after surgery with a moderate level of intensity (83%) and between one to three times per week (69%). - 42% indicated that returning to sports was among their key demands after RSA.

Table 3. *Cont.*

Authors	Implant	Outcomes		Complication (Number)	Main Conclusion
		Preoperative	Postoperative		
Schumann et al. [21]	ATSA	NR	CONSTANT SCORE (mean ± SD) GI: 70.8 ± 13.8; GII: 77.2 ± 10.6; GIII: 69.3 ± 9.7	-	The probability of being able to do sports postoperatively—if done preoperatively—is high. Long-term studies are needed to determine whether the greater loading on the joint will lead to more rapid wear and a higher rate of loosening with time.
		NR	SF-36 (mean ± SD) Physical component: GI 41.0 ± 11.2; GII: 46.2 ± 9.0; GIII: 42.2 ± 10.6; Mental component GI: 55.6 ± 9.3; GII 55.7 ± 6.4; GIII: 47.7 ± 12.9	-	
		NR	DASH SCORE (mean ± SD) GI: 76.6 ± 19.3; GII: 83.4 ± 12.7; GIII: 69.6 ± 18.6	NR	
		NR	SPADI SCORE (mean ± SD) GI: 78.6 ± 20.5; GII: 83.7 ± 16.5; GIII: 68.7 ± 19.2	-	
		34.0	ASES SCORE (mean) 78.5	-	
		6.1	VAS (mean) 0.6	NR	
		Garcia et al. [19]	ATSA		

Table 3. Contd.

Authors	Implant	Outcomes		Complication (Number)	Main Conclusion
		Preoperative	Postoperative		
Papaliotis et al. [24]	ATSA		VAS (mean average improvement) 4.3	NR	Patients who undergo TSA for primary glenohumeral arthritis can safely return to golfing activity with a significant decrease in their perceived pain level. Statistically significant findings included an increase in driving distance by 12.5 yd and an improvement in handicap by 1.4.
			CONSTANT SCORE (mean ± SD)		
		25 ± 1.9	84 ± 1.7		
			ASES SCORE (mean ± SD)		
		31 ± 1.9	72 ± 4.5	type II acromion stress fracture (1);	RTSA in senior athletes can be safely performed with good clinical results.
			ROM (mean ± SD)	postoperative infection (1),	No prominent mode of mechanical or clinical failure has been identified with short-term follow-up.
		Flexion: 78 ± 16; Abduction: 67 ± 14.6;	Flexion: 152 ± 12; Abduction: 148 ± 11.6;	postoperative dislocation (1)	
		External rotation: 26 ± 5.2	External rotation: 44 ± 5.7		
			VAS (mean ± SD)		
		7.2 ± 0.5	1.1 ± 0.5		
			SSV (mean ± SD)		
		27 ± 4.3	90 ± 4		

Table 3. Cont.

Authors	Implant	Outcomes		Complication (Number)	Main Conclusion
		Preoperative	Postoperative		
Barnes et al. [23]	RTSA		ASES SCORE (mean)	dislocation (3), aseptic loosening (1); dissociated glenosphere baseplates (1); deep infections (2); superficial infection (1)	RTSA results in good pain relief and motion, with a variety of postoperative overhead activities enjoyed by some patients who are not limited by comorbidities.
		NIR	77.5		
			ROM (mean)		
		NIR	active forward elevation: 140°, active external rotation: 48°, active internal rotation: S1		
		VAS (mean)	2.3		
Kurowicki et al. [26]	RTSA ATSA		ASES SCORE (mean)	NR	- Both TSA and RSA allow for participation in work and sports, with TSA patients reporting better overall ability to participate. - For sports involving shoulder function, TSA patients more commonly report maximal ability to participate than RSA patients.
		NIR	RTSA: 77.14 ATSA: 83.03		
Garcia et al. [20]	RTSA		ASES SCORE (mean ± SD)	None	- Patients undergoing RTSA had an 85% rate of return to 1 or more sporting activities at an average of 5.3 months after surgery. - Noncontact, high-demand activities (swimming, skiing, golf, and tennis) had lower return rates than lower demand activities. - Age greater than 70 years old was a significant predictor of decreased return to activities.
		34.3 ± 17.2	81.45 ± 17.1		
			VAS (mean ± SD)		
		6.57 ± 2.4	0.63 ± 1.7		

ATSA: anatomic shoulder arthroplasty; RTSA: reverse total shoulder arthroplasty; NIR: not reported; ASES score: American Shoulder and Elbow Surgeons Score; VAS: visual analogue scale; SF-36: Short For-36; DASH score: Disabilities of the Arm, Shoulder and Hand Score; SPADI score: Shoulder Pain and Disability Index Score; ROM: range of motion; SSV: subjective shoulder value; SD: standard deviation.

3.6. Rehabilitation Protocols

Only 5 out of 11 included papers reported the postoperative rehabilitation protocol [17,18,22,23,25]. Those authors advised a shoulder sling immobilization for the first four weeks, leaving free elbow and wrist movements. [17,18,22,23,25] In general, only passive ROM was allowed for the first 4 weeks, waiting for the sixth postoperative week to start active exercises. [17,18,22,23,25] Strengthening exercises were generally allowed from the twelfth postoperative week [18,22], even if Barnes et al. started them from the eighth [23]. On the contrary, Kolling et al. [25] permitted active mobilization and water therapy for shoulder strength and coordination from the second week after surgery. The surgical approach was evaluated in order to correlate subscapular repair to restrictions in the rehabilitative protocol. Among the five surgeons who performed the subscapularis tendon repair [16,17,21,23,25], only Kolling et al. [25] chose to limit external rotation movements to protect the reinserted tendon until the end of the second postoperative week. The postoperative rehabilitation protocols and the surgical approach are reported in Table 4.

Table 4. Rehabilitative protocols and surgical approach.

Authors	Rehabilitative Protocols	Surgical Approach
Bulhoff et al. [17]	<ol style="list-style-type: none"> 1. Abduction pillow (20°) and internal rotation (20°) for the first 4 weeks. 2. Day 1 to 6th week: daily actively assisted exercise with a physiotherapist. 3. From 6th week: active and free range of motion. 	Deltopectoral approach with subscapularis repair
Bulhoff et al. [16]	NR	Deltopectoral approach with subscapularis repair
Liu et al. [18]	<ol style="list-style-type: none"> 1. Sling immobilization for the first 4 weeks. 2. From 2nd week: passive ROM at 2 weeks. 3. From 6th week: active ROM. 4. From 12th week: strengthening exercises and prior recreational activities and work were encouraged. Restriction: avoid contact sports	NR
Kolling et al. [25]	<ol style="list-style-type: none"> 1. Sling immobilization during the night for the first 4 weeks. 2. From day 1 to 2nd week: passive motion with only limited external rotation movements to protect the reinserted subscapularis tendon. 3. From 2nd to 5th week: active mobilization and water therapy to gain shoulder strength and coordination. 4. After 12th week: resume any prior sports activities including non-contact sports. 	Deltopectoral approach with subscapularis repair
Schumann et al. [21]	NR	Deltopectoral approach with subscapularis repair
Garcia et al. [19]	NR	Deltopectoral approach
Papaliadis et al. [24]	NR	NR

Table 4. *Cont.*

Authors	Rehabilitative Protocols	Surgical Approach
Simovitch et al. [22]	<ol style="list-style-type: none"> 1. Abduction sling for the first 4 weeks. 2. From day 1 to 4th week: passive ROM and isometric exercises. 3. From 6th week: active ROM. 4. From 12th week: strengthening exercises. 5. From 16th week: return to sports. 	Deltopectoral approach without subscapularis repair
Barnes et al. [23]	<ol style="list-style-type: none"> 1. Sling immobilization for the first 4 weeks (only wrist and elbow motion allowed) 2. From 4th week: active shoulder ROM. 3. From 8th week: strengthening exercises. 	Deltopectoral approach with subscapularis repair
Garcia et al. [20]	NR Restriction: avoid contact sports.	NR
Kirowicki et al. [26]	NR	NR

NR: not reported; ROM: range of motion.

4. Discussion

In the present review, we found that the overall rate of return to sport after ATSA and RTSA in elderly patients is 82%. Specifically, 90% of patients who underwent ATSA and 77% of patients who underwent RTSA were able to practice sports again. The fact that the pooled analysis demonstrated the highest rate of return to sports in ATSA is not unexpected. Several studies demonstrated greater range of motion, higher functional outcomes scores, and improved patient satisfaction when comparing ATSA and RTSA [27,28]. Among sports commonly performed after surgery, swimming has the highest rate (84%) followed by fitness (77%), golf (77%) and tennis (69%). Therefore, the most practiced sports after surgery are the non-contact ones, probably due to a defensive attitude of patients and surgeons. Golant et al. [29] have highlighted that, in the available literature, there is an extensive variation in surgeon recommendations on activity restrictions after TSA, and that information regarding return to sports activities after shoulder arthroplasty is also lacking. In particular, they find that surgeons recommend noncontact low-load sports at the expense of contact ones. Healy et al. [30] surveyed 35 members of the American Shoulder and Elbow Surgeons regarding their recommendations for sports participation after shoulder arthroplasty. They concluded that sports that may impart high loads on the glenohumeral joint, such as football, should be avoided, whereas low-impact sports, such as cross-country skiing and swimming, may be allowed.

Papaliadis et al. [24] demonstrated that return to sports is possible, reporting a significant decrease in shoulder pain during sports activity. In this study, all patients practiced golf. Thirty one of 35 patients could return to play golf after an average time of 8.4 months postoperatively (range, 2–24 months). Fifteen patients reported subjective improvement in their ability, 12 reported no change, and only 4 reported less ability. Schumann et al. [21] evaluated the return to sports activity after TSA in 55 patients. The most practiced sports were swimming (10 patients, 20.4%), golfing (8 patients, 16.3%), cycling (8 patients, 16.3%), and fitness (8 patients, 16.3%). Six patients did not resume sport activity after TSA. Of the considered patients, 33 of the 55 were able to resume sport within six months after surgery. Another 16 patients returned to practice sport within two years after TSA. In the study of Garcia et al. [20], 85.5% of patients resumed sports activity. Low contact sports and low demand sports had the highest rate of return to practice, (fitness: 81.5%, 22/27; swimming: 66.7%, 22/33; running 57.1%, 4/7; cycling 50.0%, 6/12; golf 50%, 10/20). Of the considered cohort, 47.6% resumed sport at a higher level than preoperative, while only 10.9% did not reach their preoperative activity level.

Moreover, the papers included in this systematic review confirmed a pain reduction after shoulder surgery. In the study of Liu et al. [18], the difference between preoperative and postoperative VAS was 5.64 points. In the study of Garcia et al. [20], the postoperative VAS score was 5.64 points lower than

preoperative. Similar results were showed by Simovitch et al. [22], with a mean difference between preoperative and postoperative VAS of 6.1 points. Additionally, they showed that postoperative pain reduction was associated with an improvement of ROM and ASES scores [22]. Three studies reported the difference between preoperative and postoperative ASES and, in all of them, an improvement in postoperative values can be observed [18,20,22]. Barnes et al. [23] reported only the mean postoperative ASES which was 77.5, but even in this case, the improvement of ASES scores and VAS was associated with return to sport at the same or better preoperative level.

The present meta-analysis has shown that patients returned to sport activities at the same or a higher level in 75% of cases. This confirms that most patients undergoing shoulder arthroplasty (regardless of type) can safely return to at least one sport, with many returning to the same level of play, although a 100% guarantee should not be provided. Bulhoff et al. [17] assessed that, in their cohort, the postoperative activity levels and frequencies in sports practice were higher than before surgery. Moreover, patients were satisfied with their performances. Kolling et al. [25] selected 69 patients who clearly expressed their desire to resume sports activities after surgery and 60% of these patients were satisfied with their postoperative performance level and, within a year from surgery, 86% returned to practice sport at the same preoperative level or higher.

The postoperative rehabilitation protocol was reported in five studies [17,18,22,23,25]. Available protocols provided general information about time of immobilization and gradual recovery of shoulder motion and strength. Generally, the majority of surgeons followed similar indications: sling immobilization for at least four weeks, passive ROM for the first four weeks, active exercise from about the sixth postoperative week and strength training from the 12th postoperative week. On the contrary, Kolling et al. [25] permitted active mobilization and water therapy for shoulder strength and coordination in the second week after surgery. Unfortunately, the current literature lacks a detailed description of the rehabilitative steps and specific information about training for the athletic population. Moreover, to the best of our knowledge, no high-level evidence trials have been performed to test the efficacy of different post-operative rehabilitation protocols for patients who underwent TSA. However, some authors demonstrated that patients who received a physician-directed rehabilitation program had a significantly better range of motion as compared to patients only supervised by physiotherapists [12].

This systematic review has a few limitations including the number of studies and their heterogeneous methodological approach. Moreover, designs and implantation techniques may have varied significantly across the analyzed studies, thus reflecting the sparse available evidence on the subject and the absence of randomized controlled trials. Importantly, none of these studies mentions the abilities and experience of the surgeon. Since ATSA involves greater operative time and attention, surgical experience could be a determining factor in the decision to perform a reverse or anatomic total shoulder arthroplasty. In order to create a more homogenous cohort, future studies should account for these individual surgeon factors in the methodology. Moreover, all the included studies were affected by a high risk of bias and, in some of them, the follow-up period was quite short to detect important postoperative complications after return to sport, such as loosening or periprosthetic fractures. Patients and sports were heterogeneous as well as the postoperative rehabilitation protocol assessed. Great variability was observed in the postoperative treatment protocols following shoulder arthroplasty. Therefore, it is very difficult to identify common patterns, making it impossible to do a meta-analysis of postoperative rehabilitation protocols. Moreover, we performed the meta-analysis only on postoperative ASES and VAS scores since their preoperative data were not reported in the included studies, hindering the assessment of significant improvements of these postoperative outcomes. Finally, important postoperative clinical outcomes, such as postoperative ROM, were often not reported.

5. Conclusions

After ATSA and RTSA, elderly patients can satisfactorily resume their sports activities. The rate of return to sports following ATSA is slightly higher than RTSA, probably due to differences in the patient population, surgical indication, and biomechanical issues. Most patients are able to return to

practice sport at the same or a higher preoperative level. The most practiced sports after surgery are low contact activities such as fitness, swimming, golf, and tennis. Unfortunately, there is a lack of research data on the advantages and disadvantages of existing rehabilitation protocols and no standard of practice could be deduced. Therefore, more prospective randomized studies are needed to establish which kind of postoperative protocol is best following ATSA and RTSA.

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Review

The Influence of Preoperative Physical Activity on Postoperative Outcomes of Knee and Hip Arthroplasty Surgery in the Elderly: A Systematic Review

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Abstract: Total hip arthroplasty (THA) and total knee arthroplasty (TKA) represent two of the most common procedures in orthopedic surgery. The growing need to avoid physical impairment in elderly patients undergoing this kind of surgery puts the focus on the possibility to undertake a preoperative physical activity program to improve their fit and physical health at the time of surgery. A systematic review has been carried out with online databases including PubMed-Medline, Cochrane Central and Google Scholar. The aim was to retrieve available evidence concerning preoperative physical activity and exercise, before total knee or total hip arthroplasty in patients older than 65 years, and to clarify the role of this practice in improving postoperative outcomes. Results of the present systematic analysis showed that, for TKA, most of the studies demonstrated a comparable trend of postoperative improvement of Visual Analogue Scale (VAS), range of movement (ROM) and functional scores, and those of quality of life. There is insufficient evidence in the literature to draw final conclusions on the topic. Prehabilitation for patients undergoing TKA leads to shorter length of stay but not to an enhanced postoperative recovery. Concerning THA, although currently available data showed better outcomes in patients who underwent prehabilitation programs, there is a lack of robust evidence with appropriate methodology.

Keywords: knee; hip; arthroplasty; physical activity; elderly; prehabilitation

1. Introduction

The prevalence of osteoarthritis in the elderly population is relevant, especially for lower limb weight-bearing joints. Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are the two major surgeries for end-stage osteoarthrosis, usually advocated when all conservative treatments are inefficient. The healthcare-related economic burden is extensive for these surgeries, especially concerning postoperative hospitalization, leading in recent years to the development of several fast-track strategies aimed to improve results and decrease hospital stay expenses [1,2].

Arthroplasty aims to restore the function of the joint and soothe the pain derived from bone-on-bone arthritic conditions. After hip and knee arthroplasty, a consistent rehabilitation program is usually undertaken in order to provide the patient with the adequate strength and mobility to bear the prosthetic implant and to guarantee a correct function [1]. Isometric strengthening of the muscle

responsible for the index joint movement (gluteal muscles for the hip and quadriceps for the knee) is a key feature of postoperative rehabilitation, providing the limb with the appropriate muscular support for the mobilization of the hip or the knee. Furthermore, an antagonist stretching program is mandatory to achieve a full range of movement (ROM), avoiding postoperative stiffness and walking disabilities. In a consecutive phase, neuromuscular education to walking is advocated to eventually restore the locomotor function of the limb [3].

In recent years there has been growing interest in the possibility to prepare patients for surgery through a “prehabilitation” program, composed of strengthening and stretching exercises in the immediate preoperative period. The focus of several research projects at present is to understand whether a prehabilitation program of specific exercises or physical activities may influence and improve the postoperative outcomes of the patients. Physical exercise has been already reported to be beneficial in the knee and hip OA as a conservative treatment [4]. Activity improves function and decreases pain; thus, it is actually suggested for those patients affected, independently from the schedule of the surgery. However, it is not clear if specific exercise programs improve surgical outcomes and postoperative parameters of the patient, including the length of stay in the hospital and the quality of life. The aim of the present systematic review of the literature is to collect evidence concerning preoperative programs of activity and exercises for those patients scheduled for hip and knee arthroplasty. A specific focus of our research frame is the elderly, as there are major concerns about functional recovery and length of hospital stay in this sub-population. This intension was firstly determined from the examination of previous literature, where heterogeneity of population characteristics compromised the internal consistency of results of systematic reviews and meta-analyses [5]. The primary endpoint is to clarify the impact of specific training on subjective and objective surgical outcomes; the secondary endpoint focuses on the influence on postoperative parameters including the length of hospitalization and the quality of life of the patient.

2. Methods

The present systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines and followed the Cochrane methodology for systematic reviews [6]. However, no protocol for systematic review has been registered. Furthermore, PICO (Poipulation, Intervention, Comparison, Outcome) methodology has been used to formulate the study hypothesis. According to PICO, the following elements have been used to frame the study question:

Population—patients who are candidates for TKA or THA;

Intervention—prehabilitation; preoperative physical activity program;

Comparison—no preoperative intervention;

Outcome of interest—postoperative functional outcomes and length of stay.

2.1. Criteria for Considering Studies for This Review

The studies considered for inclusion were randomized controlled trials (RCT), prospective cohort studies (PCS), case-control studies (CCS) and case series (CS). Case reports, reviews and meta-analyses were excluded. Furthermore, basic science and in-vitro studies, biomechanical and cadaver evaluations were excluded. Studies considered should concern the preoperative physical activity in elderly patients that were scheduled for TKA or THA. According to WHO’s definition of the elderly, only studies where the average age of the cohorts was greater than 65 years were considered.

2.2. Primary Outcomes

Subjective and objective clinical measurements were considered as the primary outcome of the analysis, taking into account the clinical scores reported, which included Knee injury and Osteoarthritis Outcome Score (KOOS) Western Ontario McMaster University Osteoarthritis Index (WOMAC),

Knee Society Score (KSS) and range of motion (ROM) of the index joint. Furthermore, the outcomes of physical performance tests were considered, including the 6 min walking test (6-MWT), the time up and go test (TUG), and gait speed and distance.

2.3. Secondary Outcomes

Postoperative length of stay was the main secondary outcome considered. Furthermore, the quality of life of the patients after surgery was considered, measured through Short Form-36 (SF-36) and the quality of life section of the Knee injuries and Osteoarthritis Outcome Score (KOOS).

2.4. Search Methods for Identification of Studies

Online databases were searched for relevant articles, including PubMed-Medline, Cochrane Central and Google Scholar. The search was carried out between March and November 2019. Search strings used were the following: (“exercise” [MeSH Terms] OR “exercise” [All Fields] OR (“physical” [All Fields] AND “activity” [All Fields]) OR “physical activity” [All Fields]) AND (“aged” [MeSH Terms] OR “aged” [All Fields] OR “elderly” [All Fields]) AND (“arthroplasty” [MeSH Terms] OR “arthroplasty” [All Fields]); Prehabilitation [All Fields] AND (“aged” [MeSH Terms] OR “aged” [All Fields] OR “elderly” [All Fields]) AND (“arthroplasty” [MeSH Terms] OR “arthroplasty” [All Fields]).

No time interval was set for publication date. The studies retrieved were firstly screened by title, and where relevant, the whole abstract was read. After a first selection and exclusion of not-relevant papers, the full text of the potentially eligible articles was retrieved and read by two reviewers for eventual inclusion. Discordant opinions were solved through the consultation of a third reviewer. After the electronic search was completed, the bibliography of the relevant articles included was screened manually to identify further papers potentially missed in the electronic search. The search process is summarized in the flow diagram in Figure 1.

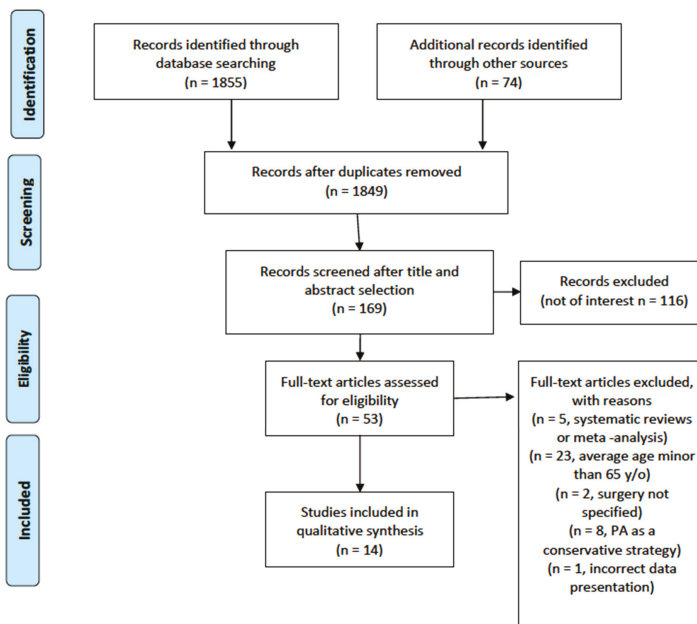


Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram. PA: Physical Activity

2.5. Data Collection and Analysis

Data were extracted from the included articles according to the primary and secondary outcomes considered for the aim of this review. After extraction, generic data concerning the paper and specific outcome data were reported in tables. The protocol of preoperative physical activity intervention was analyzed and reported in a specific table. For an appropriate presentation of data, the results were divided on the basis of the surgery (TKA or THA).

2.6. Risk of Bias Assessment

Given the heterogeneity of the included studies, two different critical appraisal tools were utilized. For randomized clinical trials, the Cochrane risk of bias assessment tool was used, providing a grade of risk (low or high risk) of bias for the index study in five elements of the study design (sequence generation, allocation concealment, blinding, incomplete data addressing and selective reporting). For non-randomized studies, the Methodological Index for Non-Randomized Studies (MINORS) score was used.

3. Results

3.1. Results of the Search

From the electronic search, a total of 1855 articles were retrieved. One of the authors (G.T.) screened the results by title and abstract and manually searched the bibliographies of the relevant papers, especially reviews and meta-analyses. Of the articles retrieved through electronic and manual search, 14 were finally included (Figure 1) [7–20].

3.2. Included Studies

Of the included studies, 12 were RCT of Level Of Evidence (LOE) I, 1 was a prospective case–control study of LOA II, and 1 was a CS of LOE IV [7]. Of these, 10 presented outcomes of TKA [7,11–19], 3 of THA and one evaluated both TKA and THA results [8–10].

3.3. Excluded Studies

Several studies retrieved were excluded for the following main reasons: average age of the cohort < 65 years [20,21], reviews or meta-analyses [22] and/or no surgery scheduled (assessment of physical activity as a conservative treatment).

3.4. Demographic Data

The included studies reported data on a total of 1175 patients, with an average age ranging from 66 to 76.9 years. A total of 1096 patients were scheduled for TKA, while 79 were scheduled for THA. Details on demographic data of the cohorts are shown in Tables 1 and 2.

Table 1. TKA.

Study	Type of Study	LOE	Number of Patients	Mean Age (y)	Type of Scheduled Surgery	Type of Intervention	Outcomes Summary
Evgeniadis et al., 2008	RCT	I	53	68.76	TKA	General strengthening exercise program 3 weeks before surgery vs. specific strengthening exercise program 8 weeks postoperatively	Preoperative SF-36 was slightly better in patients treated with preoperative strengthening. ILAS and active ROM resulted significantly improved at the termination of the program in the group treated with strengthening postoperatively
Gill et al., 2009	RCT	I	82	70.3	TKA, THA	Land-based vs. pool-based preoperative exercise programs, 6 preoperative weeks	Significant improvement in postoperative performance for both groups, although no difference occurred between groups in terms of WOMAC and SF-36
Gstoettner et al., 2011	RCT	I	38	72.8 (study group) 66.9 (control group)	TKA	Preoperative proprioceptive training	Stance stability improved significantly in the study group at 6 weeks after surgery (Biodes Stability System evaluation). No difference between study and control group occurred in postoperative (6 weeks) WOMAC and KSS
Huang et al., 2012	RCT	I	273	70	TKA	Home-based rehabilitation educational program (4 weeks before surgery)	Medical expenditure of hospital stay in the study group was significantly lower ($P = 0.001$). VAS and ROM was not significantly different in patients of both groups in the early day after surgery (5 days after admission)
Matassi et al., 2012	RCT	I	122	66 (study group), 67 (control group)	TKA	Home-based exercise program (6 weeks before surgery)	Exercise program improved the recovery of knee motion and yielded a shorter hospital stay. Differences were balanced in the long-term follow-up.
Skoffler et al., 2015	RCT	I	59	70.7 (study group), 70.1 (control group)	TKA	Progressive resistance training in the 4 preoperative weeks	Significant differences were found in the study group when compared to controls in terms of 30sCST, TUG, knee flexors strength. No difference was found in KOOS, VAS and a 100-points quality of life rating scale.
Twiggs et al., 2017	CS	IV	91	67.5	TKA	Fitbit wristband activity goals (step count)	Poor positive correlation (not statistically significant) between higher preoperative step count and hospital stay. KOOS QOL was significantly associated to step count 6-weeks postoperatively and KOOS Pain was significantly correlated to step count at preoperative and postoperative day 2–4 step count.
VanLeeuwen et al., 2014	RCT	I	22		TKA	Standard training with additional program of progressive strength training	No difference was found between groups in 6MWT and chair stand. Moreover, no difference was found in recovery time

Table 1. Cont.

Study	Type of Study	LOE	Number of Patients	Mean Age (y)	Type of Scheduled Surgery	Type of Intervention	Outcomes Summary
Williamson et al., 2007	RCT	I	181	72.4 (Acupuncture group) 70 (Physiotherapy group) 69.6 (Controls)	TKA	Supervised strengthening exercises 6 weeks before surgery	Shorter in-patient stay was observed in the physiotherapy group (1 day less than other groups)
Aytekin et al., 2018	CCS	II	44	67.8 (Prehabilitation) 69.7 (Controls)	TKA	Education and home-based exercise 12 weeks before surgery	No significant difference in VAS and KOOS occurred at 3 and 6 months between groups. Length of stay was higher for the control group. Of the intervention group, 4 subjects changed their operation decision.
Beaupre et al., 2004	RCT	I	131		TKA	Exercise and education program 4 weeks before surgery	No difference was observed in ROM and strength of the knee, pain and HRQOL

LOE: Level Of Evidence, RCT: Randomized Controlled Trial, WOMAC: Western Ontario McMaster universities Arthritis Index, CS: Case Series, CCS: Case-Control Study, ILAS: Iowa Level of Assistance Scale, THA: total hip arthroplasty, TKA: total knee arthroplasty, VAS: Visual Analogue Scale, ROM: range of motion, TUG: time up and go, 6MWT: 6-minute walking test, 30sCST: 30 s chair stand test, KOOS: Knee injury and Osteoarthritis Outcome Score, HRQOL: Health Related Quality of Life.

Table 2. THA.

Study	Type of Study	LOE	Ner of Patients	Mean Age (y)	Type of Scheduled Surgery	Type of Intervention	Outcomes Summary
Hoogboom et al., 2010	RCT	I	21	76	THA	Preoperative strengthening exercises and tailor-made activity	No difference occurred between study and control groups in length of stay and functional recovery after surgery
Oosting et al., 2012	RCT	I	30	76.9 (study group), 75 (control group)	THA	Supervised walking and functional activities from 6 to 3 weeks preoperatively	Functional improvements were observed with better results in the study group in the postoperative. TUG test and 6MWT (6 weeks after surgery)
Wang et al., 2002	RCT	I	28	68.3	THA	Preoperative customized exercise program	Exercise group showed greater stride length and gait speed at 3 weeks after surgery. Gait speed was also greater at 12 and 24 weeks, while 6MWT distance was greater at 12 and 24 weeks

ILAS: Iowa Level of Assistance Scale, THA: total hip arthroplasty, TKA: total knee arthroplasty, VAS: Visual Analogue Scale, ROM: range of motion, TUG: time up and go, 6MWT: 6-minute walking test, 30sCST: 30 s chair stand test, KOOS: Knee injury and Osteoarthritis Outcome Score, HRQOL: Health Related Quality of Life.

3.5. Total Knee Arthroplasty

3.5.1. Main intervention

Studies concerning knee arthroplasty focused on preoperative muscle strengthening or proprioceptive exercises. Timing of intervention ranged between 2 and 12 weeks before surgery. Specific training included strengthening with elastic resistance band [19], combined land-based and pool-based exercises [18], supervised proprioceptive training [17] and progressive resistance training [12,16]. Several papers intervened by instructing patients of the study group in a home-based exercise program [14,15], while several other administered supervised training sessions [13,16–19]. Some of the studies reported a continuation of the activity program in weeks 4 to 8, after surgery [16,19]. In Table 3 specific programs were summarized in comparison to control group activity.

Table 3. Protocols of intervention.

Study	Main Intervention	Control Group Intervention
Evgeniadis et al., 2008	Trunk and upper extremity elasticity elastic band (thera-band) strengthening for the 3 weeks before surgery.	No exercise before surgery, rehabilitation protocol for the 8 weeks after surgery.
Gill et al., 2009	Ingroups of 4 to 6 participants, under physiotherapist instructions: 1 h for 2 times a week for the 6 preoperative weeks. Exercises were completed at a moderate intensity between 12 and 14 on the BRPES. Home exercises were also encouraged 3 times a week. Specific program: "5 to 10 min of forward, sideways, and backward walking; 20 min pedaling a stationary exercise bike; resistance exercises; calf, hamstrings, and quadriceps stretches (2 sets of 30 s)."	Similar program schedule to land based group. Specific program: "walking and active range of movement Exercises; calf, hamstring, and quadriceps stretches (2 sets of 30 s)."
Gstoettner et al., 2011	Preoperative proprioceptive program in the 6 weeks preceding surgery: once a week, 45min training session supervised one-to-one by a physiotherapist. Daily home training instructions were given. Exercises include: slide step forward/backward, step forward/backward, single leg stance and squat.	No preoperative training
Hoogeboom et al., 2010	Supervised training twice a week for the 6 to 3 weeks preceding the index surgery. Four-phases training was administered: "First, patients started with a 5-min walk to warm up. Subsequently, they trained their lower extremity with the leg-press (sets of 10-20) through the full possible range of motion, both concentric and eccentric. Then, patients trained their aerobic capacity on a bicycle ergometer for 20-30 min. Finally, they followed a specific tailor-made training which integrates functional physical activities into the patient's daily living"	Usual preoperative and postoperative care
Huang et al., 2012	Experienced physiotherapist educated the subjects for a home-based program in a 40 min meeting 2 to 4 weeks before the index surgery. "Exercises included straight leg raising, knee setting, ankle pumping, and hip abduction with resistance"	No activity restrictions in the period before surgery. No specific training or educational, except routine.
Matassi et al., 2012	Patients were instructed for a home-based program to undertake 5 days a week in the 6 weeks preceding surgery (without the help of a therapist). Exercises included: quadriceps and hamstring stretching, isometric and isotonic quadriceps strengthening, isotonic hamstring contractions, and dynamic stepping.	Regular activities until surgery
Oosting et al., 2012	Supervised 30-min sessions twice a week for the preoperative 6 to 3 weeks. Training was tailored to the patient and his/her environment with focus on walking ability and functional daily activities.	Single supervised session 3 weeks before surgery. The session provided education on postoperative course, walking with crutches and exercises.

Table 3. *Cont.*

Study	Main Intervention	Control Group Intervention
Skoffler et al., 2015	<p>Progressive resistance training supervised sessions (60 min each) were undertaken 3 times a week in the 4 preoperative weeks and continued the program in the 4 postoperative weeks. After warm-up, the exercise session included leg press, knee extension, knee flexion, hip extension, hip abduction, and hip adduction in strength training machines.</p>	<p>Regular activities until surgery and progressive resistance training program in the postoperative period (4 weeks, as the study group).</p>
VanLeeuwen et al., 2014	<p>Standard strengthening with the adjunction of progressive strength training, including: leg press, step-up, squat, leg extension.</p>	<p>Standard strengthening</p>
Wang et al., 2002	<p>Two supervised sessions and two home-based sessions were scheduled per week, in the 8 weeks before surgery. "All exercise programs were customized to the subject and his or her level of pain, age, and general physical ability". Supervised sessions included hydrotherapy, stationary bike riding, and resistive training for thigh abduction, thigh flexion and extension, leg flexion and extension, and ankle plantar flexion.</p>	<p>Standard advices on preoperative activities given by the physiotherapist of the hospital.</p>
Williamson et al., 2007	<p>Patients were divided in groups of 6–10 patients and attended 1 h session once a week for 6 weeks before surgery. Exercise circuits were either devised or supervised.</p>	<p>Acupuncture group (II arm) received lower limb acupuncture. Control group (III arm) received an informative leaflet on preoperative exercises and advice</p>
Aytekin et al., 2018	<p>Patients allocated to the intervention group received general education about OA and TKA, with specific home-based exercise program (ankle pumping, knee range of motion, quadriceps isometric, stretching and strengthening).</p>	<p>Regular activities until surgery</p>

BRPES: Borg Rating of Perceived Exertion Scale.

3.5.2. Clinical Outcome Data

Preoperative strengthening showed a positive effect on perioperative outcomes in several of the included studies. In the study by Evgeniadis et al., SF-36 score was better for the study group, in the immediate preoperative setting, though this difference was not significant [19]. Similarly, no significant difference occurred in SF-36 in the paper by Gill et al., as well as the functional outcomes, assessed through WOMAC score [18]. A progressive resistance training program, administered in the study by Skoffer et al. [16], showed improved functional recovery in the patients of the study group assessed through TUG test, 30 s chair stand test (30sCST) and determination of knee flexion strength; however, there was no difference in KOOS, VAS and on a 100-point quality of life rating scale. Similarly, no difference was observed in WOMAC score after a preoperative proprioceptive training in another recent study [17]. Contrary to these results, the progressive strength training program advocated in the study by VanLeeuwen et al. yielded comparable functional results between groups in terms of 6MWT and chair stand [12]. Similarly, in the paper by Aytekin et al. [20], KOOS and VAS were comparable between intervention group (home-based strengthening and stretching exercises) and controls. In the case series by Twiggs et al. [7], a significant correlation was found between preoperative step count and KOOS (activity of daily living subscore) immediately before surgery ($\rho = 0.282, p < 0.05$). A trial reported that the ROM and the Iowa Level of Assistance Scale (ILAS) were significantly better in the study group after the completion of the supervised program, 8 weeks after surgery [19]. Conversely, the paper by Matassi et al. [14] reported a better recovery of knee ROM after a preoperative home-based general strengthening program. Nevertheless, a study reported no difference among groups in ROM and VAS in the early postoperative days after a pre-surgery home-based strengthening program [15]. Similarly, no difference in ROM was observed in the trial by Beaoupre et al. [11]. Hospital length of stay was assessed in five papers. The article by Huang et al. [15] reported a significantly lower medical expenditure for the patients that participated in the home-based preoperative program (7 ± 2 vs. 8 ± 1 days; $p = 0.001$). A shorter hospital stay was also reported by Matassi et al. (9.1 ± 2.1 vs. 9.9 ± 2.3 days) [14] and in the study by Williamson et al. for those patients that underwent home-based [14] or supervised (6.5 vs. 7.7 days) [13] strengthening programs. The major difference registered, though not statistically significant, occurred in the study by Aytekin et al., where the average length of stay was longer in the intervention group (5.5 ± 2 vs. 7.9 ± 2.3 days; $p > 0.05$) [20]. A prospective case series by Twiggs et al. [7] showed a poor positive correlation ($\rho = -0.114, p > 0.05$) between preoperative step count and hospital length of stay.

3.5.3. Methodological Evaluation

Nine of the included studies concerning TKA were level I RCT, and one was a level IV CS. The methodological assessment was carried out through Cochrane Risk of Bias Assessment Tool for the nine trials and the MINOR score for the non-comparative series. According to the evaluation, the studies all had some major flaws in methodology, except for one [16], where only blinding bias was considered high. Among trials, the evaluation showed that major limitations were observed concerning the blinding bias because blinding of physical activity is actually impossible to achieve. Furthermore, several studies did not describe any statistical method for addressing incomplete data, thus a high risk of bias in this field was also reported. Selective reporting was also a bias of several studies, which focused only on one or a few aspects of postoperative recovery.

3.6. Total Hip Arthroplasty

3.6.1. Main intervention

Considering the studies reporting outcomes of THA, three papers [8–10] showed outcomes of patients that underwent a program of muscular strengthening. Specifically, a personalized activity divided into progressive phases [8] was administered, either home-based or supervised [9,10]. The timing of the activity program ranged between 6 and 3 weeks before surgery, with a schedule

of two sessions per week. In Table 3 specific programs were summarized in comparison to control group activity.

3.6.2. Clinical Outcome Data

Although in one trial no difference occurred between study and control groups [8], the other two papers [9,10] reported better functional outcomes in the intervention group. Specifically, the time up and go (TUG) test and 6-minute walking test (6MWT) were better performed at 6 weeks after surgery by those patients managed with preoperative program of strengthening [9]. Similarly, 6MWT was improved in the study group at 12 and 24 weeks, and a greater stride length and increased gait speed were observed at 3, 12 and 24 weeks after surgery in those patients treated with a personalized activity program [9]. In the study by Hoogeboom et al., no difference was observed in length of stay, with an average time of 6 days in the study group (range 5–22 days) and of 6 days in the control group (range 4–7 days), with a $p = 0.228$ [8].

3.6.3. Methodological Evaluation

All the included studies concerning THA were level I RCT. The methodological assessment was carried out through Cochrane Risk of Bias Assessment Tool (Table 4). According to the evaluation, the three studies had one or more major flaws in methodology; therefore, the risk of bias within a single trial was high for the three studies. Among trials, evaluation also showed some major limitations, especially concerning allocation concealment, which was at high risk of bias. Furthermore, selective reporting was at high risk of bias for two studies [9,10] where only functional outcomes were reported, and no data concerning length of stay and perioperative outcomes were shown.

Table 4. Cochrane Risk of Bias Assessment Tool.

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Data Addressed	Selective Reporting	Other Bias
Evgeniadis, 2008	L	L	U	H	H	H
Gills, 2009	H	H	H	U	L	H
Gstoettner, 2011	L	L	H	U	L	L
Hoogeboom, 2010	L	H	H	U	H	H
Huang, 2012	L	L	H	U	H	H
Matassi, 2012	L	L	H	H	H	H
Oosting, 2012	H	H	H	H	H	H
Skoffer, 2015	L	L	H	U	L	L
VanLeeuwen, 2014	L	L	H	H	H	L
Wang, 2002	H	H	H	U	L	H
Williamson, 2007	L	L	H	U	H	L
Aytekin, 2018	H	H	H	U	L	L

L: Low, H: High, U: Uncertain.

4. Discussion

The primary endpoint of the present investigation was to assess whether a preoperative activity program impacts on the functional recovery. Concerning TKA, discordant results were reported concerning functional assessment with 6MWT and TUG, either considering studies reporting similar protocols of preoperative exercise [12,16]. However, most of the studies demonstrated a comparable trend of postoperative improvement of VAS, ROM and functional scores (KOOS and WOMAC) and those of quality of life (SF-36). Conversely, clear evidence can be observed concerning the postoperative length of stay, as all the studies analyzing length of stay demonstrated a shorter length of stay in those patients undergoing the preoperative activity program. Regarding the studies on THA, stronger

evidence is available on the positive influence of preoperative activity on functional recovery [9,10]. Conversely, length of stay was comparable between groups, although only one study reported these data. As in previous review works, these results do not achieve clinical relevance, although most are statistically significant [23,24].

The preoperative exercise programs were significantly variable and differed especially for the type of exercise, while the duration was similar, as almost all the studies reported a protocol of activity within the 6 weeks preceding the index surgery. The most relevant point concerning the activity program was supervision of the exercises by a trainer or a physical therapist. Some of the studies advocated a home-based program [9,14,15], while several other administered supervised training sessions [8,13,16–20]. A slight modification of the exercise program did not yield significant differences in results, in fact in the trial by VanLeeuwen et al. [12] no difference occurred between groups where progressive strength training was added to standard muscle strengthening. Conversely, progressive resistance training compared to daily life activities led to significantly better functional results [16]. These differences in study protocols made it difficult to compare results among the trials and prevented the authors to carry out a meta-analysis of the reported data. Although the conclusion of the single trials is often clear and the evidence seems to be defined, the summary of the results cannot be considered conclusive given the inhomogeneity of the study protocols.

Strength of the quadriceps muscle is one of the most important contributors to functioning of the knee, specifically in people with knee OA [22,25]. However, currently investigated studies failed to show the effectiveness of preoperative strengthening programs in enhancing postoperative recovery after TKA. The American College of Sports Medicine guidelines reported that to improve strength, muscle mass and endurance, exercises with a resistance of ~ 60% to 80% of the individual's 1 repetition maximum and titratable progression are required [26]. Moreover, a previous study showed that an 8-week period of exercise is necessary to produce significant improvements in pain and function and in objective measurements of muscle functioning in OA patients [27]. All the studies analyzed in the present review reported an intervention length ranging between 2 and 6 weeks, which is shorter than the minimum length, and most of them used home-based exercise programs, so it is difficult to have trustable data on whether the patients followed the indications for resistance thresholds or not. Those two factors may be responsible for not obtaining significantly better outcomes in patients who underwent prehabilitation compared to those who did not.

Concerning methodology, almost all the papers included had several biases assessed through the Cochrane Risk of Bias Assessment Tool. This evaluation highlighted that most of the trials included had several methodological flaws, especially concerning allocation concealment and blinding of the participants. However, it is relevant to understand that for active exercise programs blinding is actually impossible. Apart from this incongruity, the trials were designed in an appropriate manner and always included a control group for which normal daily activities were advised in the time before surgery. In addition, other relevant biases that affect the quality of the included trials are the selective report and the small cohorts of included patients. Especially the paucity of the cohort affects significantly the final result of a study, and the power analysis was not reported in most of the included papers. This may lead to an unpredictable overestimation or underestimation of the results. Furthermore, lack of appropriate power prevents the reader to truly understand and weigh the importance of the presented data in view of a clinical application of the evidence. Selective reporting was also a source of frequent bias, with many studies reporting data on functional outcomes (including WOMAC, KOOS) without reporting information about quality of daily life (SF-12 or SF-36) or vice-versa. This does not allow a thorough evaluation of the patients. All of these biases should be taken into account to carry out novel studies on this topic.

Potential limitations of the present systematic review include the narrow electronic research frame, as only two online databases have been searched. Furthermore, given the language capabilities of the author, only studies published in English have been retrieved and analyzed. This is a bias which may have reduced the pool of retrieved papers. However, the main strength of this study is the systematic

methodology, strictly adhering to PRISMA guidelines and PICO process for formulation of the research question. Furthermore, as an added value in comparison to previous similar works, our study strictly focuses on elderly patients, for which outcomes seem to be more homogeneous and consistent than those in other age groups. This is especially true for studies concerning total knee arthroplasty.

5. Conclusions

Although there are insufficient data to draw definitive conclusions, prehabilitation for patients undergoing total knee arthroplasty leads to a shorter length of stay, but not to an enhanced postoperative recovery. Similarly, concerning total hip arthroplasty, although currently available data showed significantly better outcomes in patients who underwent prehabilitation programs, there is a lack of robust evidence in its favor. Although the presented results do not achieve appropriate clinical relevance, it is useful to know that in small cohorts preoperative physical training shortens the length of stay in the hospital, which is a remarkable result in an era of increased attention to healthcare expenses. Thus, considering prehabilitation measures are non-invasive and low-cost activities, it would be worthwhile to suggest them to patients undergoing total joint arthroplasty.

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Review

The Role of Physical Activity as Conservative Treatment for Hip and Knee Osteoarthritis in Older People: A Systematic Review and Meta-Analysis

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Abstract: The aim of this systematic review and meta-analysis is to determine the role of physical activity as a conservative treatment for older people with knee or hip osteoarthritis. The effect on pain, physical function, stiffness, quality of life, and dynamic balance of Aquatic Exercise, Land-based Exercise, and Sports were compared in a specific population composed of osteoarthritic patients aged 65 or over. A systematic search using Pubmed-Medline, Google Scholar, and the Cochrane Library was carried out to select randomized clinical trials, observational studies, or case series that evaluated outcome measures after physical activity. Twenty randomized controlled trials (RCTs) and two case series were included in this review. Four trials were at low risk of bias (A), 12 at unclear risk of bias (B), and four at high risk of bias (C). Compared to controls, Aquatic Exercise, Land-based Exercise, Tai Chi, and Yoga showed a small to high effect for improving pain, physical function, quality of life, and stiffness. Active exercise and sport are effective to improve pain and physical function in elderly people with osteoarthritis. Nevertheless, further studies are required to validate the use of land-based exercise, aquatic exercise, or sport to treat the symptoms of older adults that suffer from knee and hip osteoarthritis.

Keywords: physical activity; active exercise; sport; land-based; aquatic; knee or hip osteoarthritis; older people; systematic review; meta-analysis

1. Introduction

Osteoarthritis (OA) is a chronic progressive disease that represents a considerable cause of impairment in elderly people [1]. It is characterized by pain, reduction of physical function with decreased range of motion (ROM), joint rigidity and swelling, muscle weakness, and joint instability [2,3]. All these conditions lead to impaired quality of life with worsening to achieve daily activities and disability, especially in older adults [4]. Knee and hip are commonly affected by OA [5] because they represent the joints most involved in heavy weight-bearing and increased activity [6,7]. The prevalence of OA is higher in women and elderly people [8]. OA requires remarkable healthcare resources and involves considerable social costs for treatment, due to its progressive and chronic condition, and those demands are bound to increase with an aging population [9]. Conservative treatment for OA consists of pharmacologic therapy (Non-Steroidal Anti-Inflammatory Drugs, cyclooxygenase inhibitors, oral or transdermal opioid, acetaminophen), injective therapy (corticosteroids, Hyaluronic

acid, Platelet-Rich Plasma or Adipose-Derived Stem Cell), supportive therapy (glucosamine or chondroitin), physical therapy (Electrical Nerve Stimulation, Pulsed Electromagnetic Field, Laser Therapy, Therapeutic Ultrasound), braces, orthoses, active exercise (aquatic or land-based), physical and sport activity [10–12]. We focused our research on active exercise and sports that have been determined to be effective in pain relief, maintenance of joint integrity, and muscle strength, improvement in physical function, and lessening deformity and instability [13]. Active exercise has been proved to increase physical function and reduce knee and hip pain and disability, improving general health status and quality of life [14,15]. The role of exercise or sportive activities is to avoid or delay the necessity to recur to the knee or hip joint replacement, which must be reserved just for the final stage of OA [16], which is characterized by severe pain and deformity. Land-based exercise programs such as aerobic, strengthening, and resistance training are effective therapies for knee and hip OA [17,18]. Furthermore, the increase of lower limb muscular strength and the improvement of balance and coordination of movements are effective in achieve compensatory functional stability in older people with advanced OA in order to reduce the risk of falling [19,20]. Aquatic exercise profits by the weight-relieving properties of water to obtain pain relief, to allow easier joint movement improving physical function, to reduce muscle stiffness and to cause muscle relaxation in patients with OA [21,22]. In contact sports, there is a higher incidence of significant joint injuries or progression of osteoarthritis [23]; however, low-impact sports are suggested as a physical treatment for osteoarthritis because they prevent from maximum stress and enhance muscle strength and joint stability [24]. Therefore, sports are effective both in the prevention and in the treatment of OA, but they have to be modulated on the individual patient's physical abilities. The evidence on comparative effectiveness on pain and physical function of different types of active exercise or sport interventions or older adults with knee or hip OA is still poor. In fact, an adequate activity to conservatively treat those patients obtaining clinical benefits has not yet been identified. Therefore, the aim of this systematic review and meta-analysis is to determine the efficacy of physical activity as a conservative treatment for elderly people with knee or hip OA. The primary endpoint is to assess the effect on pain, physical function, stiffness, quality of life, and dynamic balance outcomes of different active exercise and sports. The secondary endpoint is to establish the specific benefits on the selected outcomes of the single intervention, to try to evaluate if there is an exercise or sport that leads to better enhancement in physical capacity and quality of life of older osteoarthritic adults.

2. Materials and Methods

A systematic review and meta-analysis were carried out using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [25]. The review was planned and conducted following the PRISMA checklist (Supplementary Materials Table S1). In this review, we included randomized clinical trial, observational studies, or case series, which evaluated the role of sport or exercises as a conservative treatment for patients aged 65 or over with all degrees of the knee and hip OA.

2.1. Criteria for Considering Studies for This Review

According to the WHO definition of the elderly, studies with patients with a mean age of 65 or over both in the experimental group(s) and the control group, if present, were included in the review. Studies that compared effects on pain, physical function, and physical performance of the aquatic exercise, land-based exercise, or sports with a control group were included in the review. In the randomized clinical trial, the patients in the control group had to receive usual care or no intervention. We excluded studies that investigated physical activity in the prevision of hip or knee surgery or after hip or knee replacements.

2.2. Search Methods for Identification of Studies

A systematic literature search was performed using the following databases: Pubmed-Medline, Google Scholar, and the Cochrane Library. For Pubmed we used the following search strategy: (“exercise”[MeSH Terms] or “exercise”[All Fields] or (“physical”[All Fields] and “activity”[All Fields]) or “physical activity”[All Fields]) and (“knee osteoarthritis”[MeSH Terms] or “knee osteoarthritis”[All Fields]); (“exercise”[MeSH Terms] OR “exercise”[All Fields] or (“physical”[All Fields] AND “activity”[All Fields]) or “physical activity”[All Fields]) AND (“hip osteoarthritis”[MeSH Terms] or “hip osteoarthritis”[All Fields]). The reference list of the identified articles was screened manually for further publications. After duplicates removed, the abstracts of all studies eligible were independently examined by two review authors (G.P. and B.Z.). Any uncertainties or disagreements (17 in total) were discussed with the third reviewer (R.P.) to reach a consensus. Two reviewers (G.P. and B.Z.) screened the full articles in order to determine those to include in the review and quantitative analysis.

2.3. Data Collection, Analysis, and Outcomes

Data extraction was independently produced by two reviewers (G.P. and B.Z.). We extracted the following study characteristics: authors, year of publication, type of study, level of evidence, numbers of participants in the intervention or control group integrated with age, gender and Body Mass Index (BMI), joint(s) involved, intervention in the study and in the control group, primary and secondary outcome measures, follow-up, and results. Any uncertainties or disagreements (four in total) were discussed with the third reviewer (R.P.) to reach a consensus. Outcomes included the severity of pain, which was measured on a visual analog scale (VAS), on the pain scale of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) or the Knee injury and Osteoarthritis Outcome Score (KOOS) pain scale. Physical function was calculated by the WOMAC physical function scale, the KOOS ADL (function in daily living) scale, the 6-min walking test (6-MWT), the sit to stand test and range of motion (ROM) of the considered joint. Stiffness was checked with the WOMAC stiffness scale. The quality of life of the patients was measured through Short Form-36 (SF-36) or Short Form-12 (SF-12), and KOOS Quality of Life (QOL). Finally, the dynamic balance was assessed using the time up and go test (TUG).

2.4. Risk of Bias Assessment

Two review authors (G.P. and B.Z.) independently assessed the risk of bias of the randomized controlled trial (RCT) using the Cochrane Risk of Bias Tool [26]. We checked the following criteria: sequence generation, allocation concealment, blinding, incomplete data addressed, free of selective reporting, and free of other bias. Each domain was classified as presenting high risk of bias, low risk of bias, or unclear risk of bias. Then the trials were allocated to one of the following groups: low risk of bias if five or six criteria were judged adequate, unclear risk of bias if three to four criteria were judged as adequate or high risk of bias if less than three criteria were judged adequate. Two reviewers (G.P. and B.Z.) used the Methodological Index for Non-Randomized Studies (MINORS) score [27] to estimate the methodological quality of non-randomized studies. It consists of 8 items for non-comparative studies and 12 items for comparative studies. The score for each item ranges from 0 to 2, for a total maximum of 24 points.

2.5. Statistical Analysis

The quantitative data analysis was performed using the Review Manager (RevMan) software (Version 5.3, Cochrane Collaboration 2014, Copenhagen, Denmark). The data were pooled if at least two studies presented similar and comparable outcomes. A meta-analysis was performed to determine the effect of the different types of physical activity on pain, physical function, quality of life, stiffness, and dynamic balance. All continuous data were reported as mean difference (MD) with 95% confidence intervals when all the trials used the same score; otherwise, the standardized mean difference (SMD)

with 95% confidence intervals was used when the analyzed scores were similar but not identical. Negative values of the mean difference or standardized mean difference proved the advantage of the experimental group. Heterogeneity was determined using the I^2 test. A fixed-effect model was conducted if the I^2 test demonstrated low heterogeneity ($I^2 < 55\%$); for I^2 greater than or equal to 55%, a random-effect model was performed.

2.6. Quality Assessment

To assess the quality of the evidence of the outcomes presented in the reported trials, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) was performed [28]. It consists of the following five items: risk of bias, inconsistency, indirectness, imprecision, and other considerations. Each domain was defined as not serious, serious, or very serious. The resulting quality assessment of the evidence was classified as high, moderate, low, or very low.

3. Results

3.1. Results of the Search

The literature search identified 2445 articles. Of these, 1817 were screened on title and abstract after the removal of duplicates. One hundred sixty-nine articles were read in full text, and 147 of those were excluded for the following reasons: not mainly evaluating physical activity intervention ($n = 45$), patients aged less than 65 years ($n = 67$), not specified joints that suffered from OA ($n = 14$), protocols of RCT ($n = 18$), and case reports ($n = 3$). Thus, 22 articles that met the inclusion criteria were included in this review. Finally, 19 articles were included in the meta-analysis (Figure 1).

3.2. Included and Excluded Studies

The studies were 20 RCTs and two case series. One case series involved Baduanjin, while the other one evaluated exercise [29]. Of the RCTs, six studies checked sports activity $n = 4$ Tai Chi [30–33], $n = 2$ yoga [34,35]. The remaining RCTs were focused on water-based and land-based exercises: there were three studies with three arms (hydrotherapy, land-based exercise and control group) [36–38], four studies that compared only hydrotherapy with controls [39–42], and seven studies that only evaluated land-based exercises [43–49].

3.3. Demographic Data

The overall number of participants in all the studies was 1504, allocated to either intervention or control groups. The mean age of the participants ranged from 65 to 78.9 years. All studies showed a higher female percentage (ranging from 50 to 100%) of included patients. Only one study [35] did not describe gender distribution in the groups. BMI ranged between 23.7 and 33.6. All demographic data are compiled in Table 1.

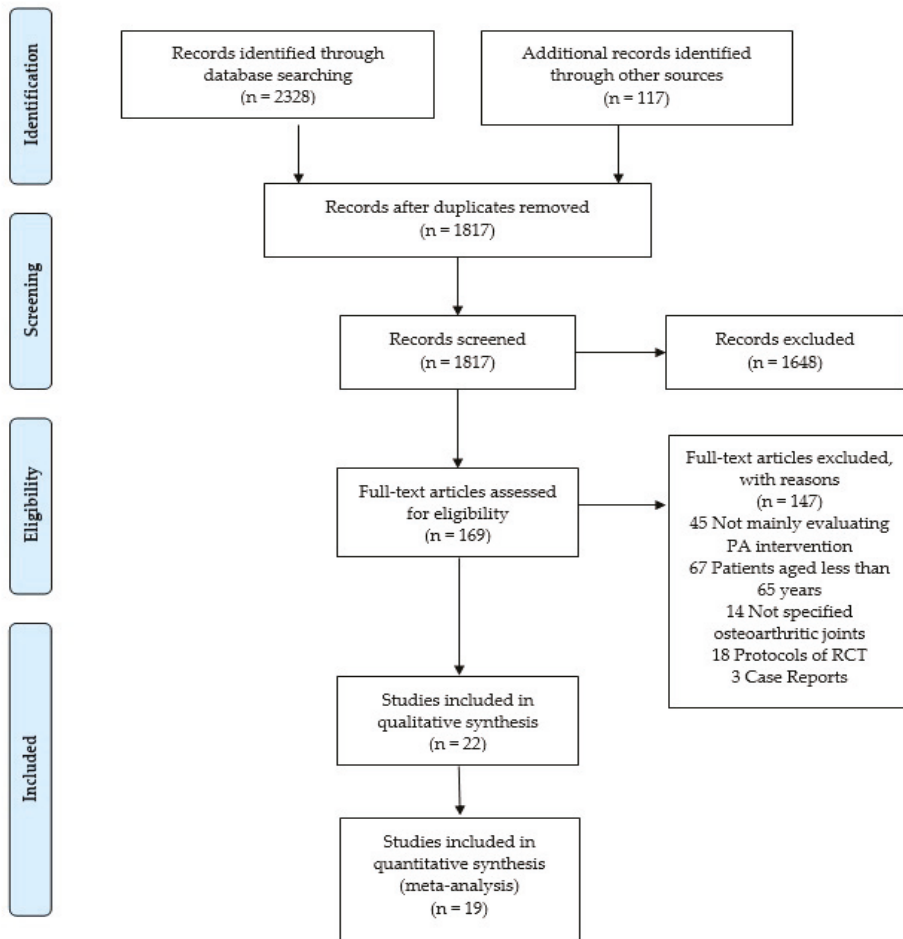


Figure 1. Flowchart of the article selection process.

Table 1. Demographic data of the included studies.

Author (Year)	Type of Study	LOE	Study Group				Control Group				Joint/s
			n	Age	Sex	BMI	n	Age	Sex	BMI	
Arnold et al. (2010) [42]	RCT	I	Aquatic and education: 28	73.2 y	71.4% F, 28.6% M	29.2	25	75.8 y	64% F, 36% M	30	hip OA
			Aquatic: 26	74.4 y	77% F, 23% M	30.4					
Bearne et al. (2011) [43]	RCT	I	24	65 y	62.5% F, 37.5% M	27.3	24	67 y	79% F, 21% M	26.9	hip OA
Bezalel et al. (2010) [44]	RCT	I	25	73.8 y	68% F, 32% M	/	25	73.7 y	80% F, 20% M	/	knee OA
Brismee et al. (2007) [31]	RCT	I	22	70.8 y	86.4% F, 13.6% M	28	19	68.8 y	78.9% F, 21.1% M	27.7	knee OA
Casilda-López et al. (2017) [40]	RCT	I	17	65.62 y	100% F	31.69	17	66 y	100% F	33.65	knee OA
Cheung et al. (2014) [34]	RCT	I	18	71.9 y	100% F	29.1	18	71.9 y	100% F	28.8	knee OA
Cheung et al. (2016) [35]	RCT	I	Yog: 32	68.9 y	/	29.8	23	71.8 y	/	27.8	knee OA
			Exercises: 28	74.4 y	/	29.2					
Doi et al. (2008) [46]	RCT	I	63	67.4 y	76% F, 24% M	24.8	58	71.2 y	72% F, 28% M	24.3	knee OA
Foley et al. (2003) [37]	RCT	I	Aquatic: 35	73 y	43% F, 57% M	/	35	6.8 y	57% F, 43% M	/	hip and knee OA
			Land-based: 35	69.8 y	49% F, 51% M	/					
Fransen et al. (2007) [30]	RCT	I	Aquatic: 55	70 y	73% F, 27% M	30	41	69.6 y	83% F, 17% M	30.7	hip and knee OA
			Tai chi: 56	70.8 y	68% F, 32% M	29.6					
Hale et al. (2012) [39]	RCT	I	23	73.6 y	74% F, 26% M	/	16	75.7 y	75% F, 25% M	/	hip and knee OA
Huang et al. (2017) [45]	RCT	I	128	68.07 y	79% F, 21% M	24.11	122	67.42 y	80% F, 20% M	25.01	knee OA
Hurley et al. (2007) [48]	RCT	I	Individual rehabilitation: 146	66 y	71% F, 29% M	30	140	67 y	68.5% F, 31.5% M	30.3	knee OA
			Group rehabilitation: 132	68 y	71% F, 29% M	30.18					
Lee et al. (2009) [32]	RCT	I	29	70.2 y	93.1% F, 6.9% M	26	15	66.9 y	93.3% F, 6.7% M	26	knee OA
Lund et al. (2008) [38]	RCT	I	Aquatic: 27	65 y	83% F, 17% M	27.4	27	70 y	66% F, 34% M	26.1	knee OA
			Land-based: 25	68 y	88% F, 12% M	23.7					
Marconcin et al. (2017) [47]	RCT	I	35	70.3 y	80% F, 20% M	32.3	32	67.8 y	59.4% F, 40.6% M	30.1	knee OA
Taglietti et al. (2018) [41]	RCT	I	31	67.3 y	74.2% F, 25.8% M	29.2	29	68.7 y	62.1% F, 37.9% M	30.4	knee OA
Takacs et al. (2017) [49]	RCT	I	20	66.1 y	95% F, 5% M	28.5	20	67.1 y	65% F, 35% M	28.9	knee OA
Tsai et al. (2013) [33]	RCT	I	28	78.89 y	78.6% F, 21.4% M	/	27	78.93 y	66.7% F, 33.3% M	/	knee OA
Wang et al. (2011) [36]	RCT	I	Aquatic: 26	66.7 y	84.6% F, 15.4% M	/	26	67.9 y	84.6% F, 15.4% M	/	knee OA
			Land-based: 26	68.3 y	88.5% F, 11.5% M	/					
An et al. (2013) [50]	CS	IV	22	66 y	86% F, 14% M	25	/	/	/	/	knee OA
Bove et al. (2017) [29]	CS	IV	7	66 y	71.5% F, 28.5% M	30.5	/	/	/	/	knee OA

RCT: Randomized Clinical Trial; CS: Case Series; LOE: Levels of Evidence; BMI: Body Mass Index; OA: Osteoarthritis; n: Number of participants; y: years; F: female; M: male.

3.4. Clinical Outcome Data

Seventeen studies included patients with knee OA alone, two studies included patients with hip OA alone, and the remaining three studies included patients with both knee and hip OA. The outcome measures evaluated in the included articles were the Western Ontario and McMaster Universities Arthritis Index (WOMAC) in 17 articles, the 6-min walk test (6-MWT) in seven articles, Knee Injury and Osteoarthritis Outcome Score (KOOS) in three articles, Visual Analog Scale (VAS) in seven articles, Short Form-36 (SF-36) in four articles, Short Form-12 (SF-12) in four articles, sit to stand test and timed up and go test in five articles (Table 2).

Table 2. Clinical outcome data of the included studies.

Author (Year)	Intervention(s)	Control	Primary Outcome Measure	Secondary Outcome Measure	Follow-Up	Results
Arnold et al. (2010) [42]	Aquatic and education: aquatic exercise twice a week with once-a-week group education for 11 weeks; Aquatic two weeks aquatic exercise for 11 weeks	no intervention	Berg Balance Scale, 6-MWT, Timed Up and Go Test	PASE score, AIMS-2 score	11 weeks	Significant improvement in fall risk factors ($p = 0.038$) with the combination of aquatic exercise and education.
Bearne et al. (2011) [43]	Ten 75-min group exercise and self-management sessions (twice a week for five weeks)	no intervention	WOMAC physical function	WOMAC pain, WOMAC total score	Six weeks and six months	No between-group differences in any outcome measure.
Bezaled et al. (2010) [44]	Group education program once a week for four weeks, followed by a self-executed home-based exercise program	six 20-min sessions of short-wave diathermy	WOMAC total score	Sit to stand test, Timed up and go test	four and eight weeks	Significant improvement in the timed up and go test and WOMAC total ($p < 0.01$) in the exercise group.
Brismee et al. (2007) [31]	Six weeks of group Tai Chi sessions, 40 min/session, three times a week, followed by another six weeks of home-based Tai Chi training	three 40-min group sessions per week for six weeks	WOMAC pain, VAS	WOMAC stiffness and physical function	3, 6, 9, 12, 15, and 18 weeks	Less overall pain and better WOMAC physical function with Tai Chi ($p = 0.0089$ and 0.0157 , respectively).
Casilda-Lopez et al. (2017) [40]	Eight-week dance-based aquatic exercise program	global aquatic exercise program	WOMAC total score	6-MWT and VAS	Eight weeks and Three months	Postintervention differences in the WOMAC pain and aggregate ($p = 0.002$ and $p = 0.048$) in favor of the experimental group.
Cheung et al. (2014) [34]	Eight-week Hatha yoga intervention involving group and home-based exercise sessions	no intervention	WOMAC total score	SPPB, SF-12	Four weeks, eight weeks and 20 weeks	Improvement in WOMAC pain $p = 0.01$ and stiffness ($p = 0.02$) in the intervention group.
Cheung et al. (2016) [35]	Yoga: one 45-min class per week for eight weeks and additional 30 min/day, four times/week of yoga practice at home; Exercises: eight weekly group-based classes	no intervention	WOMAC total score, VAS	SPPB, SF-12	Four and eight weeks	Yoga group presented improvements in WOMAC TOTAL ($p = 0.001$) and VAS scores ($p = 0.03$) compared to exercises group.
Doi et al. (2008) [46]	Four sets of 20 repetitions of quadriceps exercise every day (knee extension movements while sitting on a chair or in a supine position)	NSAIDs	WOMAC total score and VAS	SF-36	Eight weeks	Improvements in total WOMAC, SF-36 and VAS: all $p < 0.001$ in the exercises group; WOMAC and VAS at $p < 0.001$ and SF-36 at $p < 0.03$ in the control group.
Foley et al. (2008) [37]	Three water based, or three gym-based exercise sessions a week for six weeks, including a short warm up period, lower limb stretches, and a set of resistance exercises	no intervention	WOMAC total score, 6-MWT	SF-12	Six weeks	Walking speed and distance increased in the hydrotherapy and gym groups (both $p < 0.001$). No significant changes for WOMAC function or stiffness.
Franssen et al. (2007) [30]	Aquatic or Tai Chi program (with a preliminary 10-min warm-up session): 1 h, twice a week for 12 weeks	no intervention	WOMAC pain and physical function	SF-12, DASS21	12 and 24 weeks	Improvements of 6.5 and 10.5 for pain and physical function scores with hydrotherapy and improvements of 5.2 and 9.7 with Tai Chi.
Hale et al. (2012) [44]	Water-based exercise classes twice weekly for 12 weeks	community-based computer-skills training program	PTA	Step Test, Timed Up and Go Test, WOMAC total score	12 weeks	No statistically significant between-group differences were found for any outcome measured.

Table 2. Contd.

Author (Year)	Intervention(s)	Control	Primary Outcome Measure	Secondary Outcome Measure	Follow-Up	Results
Huang et al. (2017) [45]	Quadriceps isometric contraction exercise (two sets of exercises in the morning and evening)	local physiotherapy and oral NSAIDs	WOMAC total score, VAS	/	One and three months	Significant improvement of WOMAC and VAS score in the experimental group ($p < 0.05$).
Hurley et al. (2007) [48]	12 supervised sessions that combined discussion on specific topics regarding self-management and coping, with an individualized, progressive exercise regimen	no intervention	WOMAC physical function	WOMAC pain, WOMAC total score	Six weeks and six months	Individual and group rehabilitated participants had better WOMAC score ($p = 0.01$) than control group.
Lee et al. (2009) [52]	Eight weeks of group Tai Chi Qigong sessions, with 60 min per session twice a week	no intervention	SF-36	WOMAC total score, 6-MWT	Eight weeks	Improvements in SF-36 ($p = 0.010$) and 6-MWT ($p = 0.005$) in the Tai Chi group.
Lund et al. (2008) [38]	Aquatic and land-based exercise programs for eight weeks with 2 sessions per week	no intervention	KOOS function and pain, VAS	Muscle Strength	Eight weeks and three months	Only in the land-based exercise group a decrease of pain was detected ($p = 0.039$). There were no significant differences between groups for KOOS.
Marconcini et al. (2017) [47]	PLEZNO program: 90-min intervention twice a week for 12 weeks	no intervention	KOOS pain	KOOS function and total score, 6-MWT	12 weeks	Significant clinical improvement was found for all KOOS (larger than 10 points) and in the 6-MWT ($p = 0.035$) in the exercise group.
Taglietti et al. (2018) [41]	Aquatic program twice a week for eight weeks	educational program: once a week for eight weeks	WOMAC total score, VAS	SF-36, Timed up and go test, Yesavage Geriatric Depression Scale	Three months	WOMAC pain reduced in favour of the aquatic exercise group ($p = 0.021$). No differences for the outcome's functional mobility or depression.
Takacs et al. (2017) [49]	Ten weeks of exercises targeting dynamic balance and strength performed four times per week	no intervention	CB&M, WOMAC physical function	Muscle Strength	10 weeks	Improvements in self-reported pain ($p = 0.005$), physical function ($p = 0.002$), and fear of movement ($p = 0.01$) in the training group.
Tsai et al. (2013) [33]	Three sessions a week of Tai Chi exercise (12-form Sun Tai Chi) for 20 weeks	no intervention	WOMAC pain	WOMAC physical function and stiffness, timed up and go test and Sit to stand test	21 weeks	WOMAC pain ($p < 0.001$), physical function ($p = 0.001$) and stiffness scores ($p = 0.001$) improved in the Tai Chi group.
Wang et al. (2011) [36]	Aquatic/hand-based exercise protocol with a 60-min flexibility and aerobic training class, three times a week for 12 weeks	no intervention	KOOS total score, 6-MWT	knee ROMs	Six and 12 weeks	Aquatic and land group presented less pain than control group (respectively $p < 0.001$ and $p = 0.002$).
An et al. (2013) [50]	Short-term Baduanjin exercise: 30-min sessions five times a week for one year	/	WOMAC total score, SF-36	6-MWT	one year	WOMAC pain, stiffness and physical function subscales, SF-36 body pain and 6-MWT were significantly improved.
Bove et al. (2017) [29]	16 sessions of task-specific training at a frequency of two visits per week	/	KOOS total score	30-Second Chair Rise, Timed Stair Climb Test, Floor Transfer Test	Four, six, and eight weeks	Improvements in patient-rated and performance-based outcomes.

PASE: Physical Activity Scale for the Elderly; AIMS-2: Arthritis Impact Measurement Scales 2; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: Visual Analog Scale; 6-MWT: 6 min walk test; SPPB: Short Physical Performance Battery SF-12: Short Form-12; NSAIDs: Nonsteroidal anti-inflammatory drugs; DASS21: Depression, Anxiety and Stress Scale; PPA: Physiological Profile Assessment; KOOS: Knee Injury and Osteoarthritis Outcome Score; CB&M: Community Balance and Mobility Scale; ROM: Range of Motion.

3.5. Methodological Evaluation

Using the Cochrane risk of bias tool for RCTs, sequence generation was considered adequate in 16 articles (80%), allocation concealment was graded as adequate in 15 studies (75%), blinding was inadequate in 15 trials (75%), outcome data addressed were regarded adequate in 16 articles (80%), reporting of selective outcome was judged as adequate in 14 (70%) trials, and the likelihood of other sources of bias was adequate in 10 (50%) of the studies. In conclusion, four trials were at low risk of bias (A), 12 included studies were at unclear risk of bias (B), and four studies were at high risk of bias (C) (Table 3). The MINORS score was calculated for two case series [29,50] included in the review. Only eight items were evaluated because the two studies were non-comparative (Table 4).

Table 3. Cochrane risk of bias tool for randomized controlled trials.

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Data Addressed	Free of Selective Reporting	Free of Other Bias	Risk of Bias
Arnold et al. (2010)	L	L	H	L	U	L	B
Bearne et al. (2011)	L	U	H	L	U	U	C
Bezalel et al. (2010)	L	L	H	U	U	U	C
Brismee et al. (2007)	L	U	H	L	L	U	B
Casilda-López et al. (2017)	L	L	U	L	U	U	B
Cheung et al. (2014)	L	L	H	L	L	U	B
Cheung et al. (2016)	L	L	H	L	L	L	A
Doi e al. (2008)	L	L	H	H	L	U	B
Foley et al. (2003)	L	L	U	L	L	U	B
Fransen et al. (2007)	L	L	U	L	L	U	B
Hale et al. (2012)	L	L	U	U	L	L	B
Huang et al. (2017)	U	U	H	L	H	H	C
Hurley et al. (2007)	U	L	H	U	L	L	B
Lee et al. (2009)	L	L	H	L	L	L	A
Lund et al. (2008)	U	L	U	L	L	L	B
Marconcin et al. (2017)	H	U	H	L	L	U	C
Taglietti et al. (2018)	L	L	H	L	L	L	A
Takacs et al. (2017)	L	L	H	L	U	L	B
Tsai et al. (2013)	L	L	H	L	L	L	A
Wang et al. (2011)	L	U	H	L	L	L	B

Table 4. MINORS (Methodological Index for Non-Randomized Studies) score.

Study	Stated Aim	Inclusion of Patients	Collection of Data	Endpoints Appropriate to the Aim	Unbiased Assessment of the Study Endpoint	Follow-Up	Loss to Follow Up Less Than 5%	Prospective Calculation of the Study Size	Total
Am et al. (2013)	2	1	2	2	1	2	2	0	12
Bove et al. (2017)	2	1	2	2	1	1	2	0	11

3.6. Studies Included

3.6.1. Double Study Group

Five studies with two study groups were identified. Wang et al. [36] recruited 78 patients that were divided into the aquatic group, the land group, and the control group. The study demonstrated that patients in both exercise groups showed pain reduction over time. More specifically, the aquatic and the land groups presented significantly less pain than the control group at week 12 (both $p < 0.001$) and at week 6 ($p < 0.001$ for aquatic and $p = 0.002$ for land). Comparing the aquatic group with the land group, they did not show any significant difference in pain reduction at weeks 12 and 6. Foley et al. [37] evaluated 105 participants with hip or knee OA, that received water-based exercise sessions, gym-based exercise sessions, or were allocated to the control group. At follow up, walking speed and distance increased in the hydrotherapy and gym groups (both $p < 0.001$), but not in the control group. However, they did not find a significant difference between the two intervention groups for increases in physical function. Furthermore, the WOMAC pain significantly declined in the hydrotherapy group, but they did not demonstrate significant changes from baseline or between groups for WOMAC function or stiffness. Lund et al. [38] compared the efficiency of aquatic exercise and a land-based exercise program with control in 79 patients with knee OA. Only in the land-based exercise group, a decrease of pain was detected ($p = 0.039$). There were no significant differences between groups for KOOS. Fransen et al. [30] assigned 152 older patients with chronic hip or knee OA to hydrotherapy group, Tai Chi group, or a waiting list (control group). It has been shown improvements of 6.5 and 10.5 for pain and physical function scores with hydrotherapy and improvements of 5.2 and 9.7 with Tai Chi, compared with controls. Only the hydrotherapy group showed significant improvements in pain scores, SF-12, and the measures of physical performance. Cheung et al. [51] evaluated the effects of yoga and aerobic/strengthening exercises on knee OA, compared with the education control group. Patients in the yoga group presented improvements in WOMAC TOTAL ($p = 0.001$) and VAS scores ($p = 0.03$) compared to patients in exercises group.

3.6.2. Land-Based Exercise

In a study by Bearne et al. [43], 48 people with hip OA were divided into the rehabilitation group or the control group. At the term of the program, the WOMAC total score improved with a moderate effect size. But there were no differences between the two groups in any outcome measure. Bezalel et al. [44] randomly assigned 50 patients with knee OA to an exercise group or a short-wave diathermy control group. At follow-up, participants in the study group showed significant improvement in the get-up-and-go test and the WOMAC total, pain, and disability scores compared to the controls ($p < 0.01$). Huang et al. [45] enrolled 250 patients with knee OA. The test group underwent quadriceps isometric contraction exercise, while in the control group local physiotherapy and oral NSAIDs were used. At three months, WOMAC and VAS scores showed significant progress in the exercise group compared to the controls (both $p < 0.05$). In a study by Doi et al. [46], 121 patients with knee OA were allocated to an exercise group and an NSAID group. The participants in both groups presented improvements in the totality of the scores (WOMAC, SF-36, and VAS at $p < 0.001$ in the exercises group; WOMAC and VAS at $p < 0.001$ and SF-36 at $p < 0.03$ in the control group), although these increases were not statistically significant between the two groups. Therefore, they

showed the “noninferiority” of exercises compared with NSAIDs as a therapy for knee OA. Marconin et al. [47] allocated 67 patients aged 60 years or older with knee OA to a self-management and exercise intervention or an educational intervention. In the self-management and exercise group, significant improvements in all KOOS dimensions (larger than 10 points) and in the 6 MWT ($p = 0.035$) were found. In a study by Hurley et al. [48], 418 practices were randomly assigned to three groups to receive usual primary care, usual primary care plus individual rehabilitation or usual primary care plus rehabilitation in groups. Six months after the end of the schedule, the WOMAC-function scores for the individual rehabilitation and group rehabilitation classes were significantly better compared with usual care ($p = 0.01$). Although the improvements were similar for participants that made individual or group rehabilitation. Takacs et al. [49] checked 40 participants that underwent exercises targeting dynamic balance and strength or no intervention. They showed significant improvement in WOMAC physical function in the exercise group (within-group $p = 0.002$; between-group $p = 0.016$). Moreover, self-reported knee pain and fear of movement results were better in the exercise group ($p = 0.005$ and $p = 0.01$, respectively) compared to the control group. In a study by Bove et al. [29], seven patients underwent a novel task-specific training approach to exercise therapy for chronic knee pain, composed of sit to stand, floor transfer, and ascending and descending stairs training. After the treatment, the participants demonstrated important improvements in both patient-rated outcomes (for example, KOOS) and performance-based outcomes.

3.6.3. Aquatic Exercise

In a study by Hale et al. [39], 39 persons with hip or knee OA and at risk for falling underwent a water-based program (intervention group) or a time-matched computer training program (control group). After the 12-week intervention, they proved that water-based exercise did not decrease falls risk compared with a computer skills training class, with no significant disparities between the two groups for the primary outcome (PPA score) or any of the secondary outcomes measured. Casilda-Lopez et al. [40] divided 34 obese women with knee OA into a dance-based aquatic exercise program (experimental group) and a global aquatic exercise program (control group). Postintervention, they found significant differences between groups in the WOMAC pain and aggregate ($p = 0.002$ and $p = 0.048$, respectively) in favor of the aquatic dance group. Taglietti et al. [41] allocated 60 patients with knee OA to an aquatic exercise group, and an educational program group. After the treatment, they presented a significant decrease of WOMAC pain for the aquatic exercise group compared to the educational program group ($p = 0.021$). Furthermore, the WOMAC function decreased significantly in the aquatic exercise group compared to baseline ($p = 0.020$). Moreover, improvements in quality of life were detected in the aquatic exercise group ($p < 0.001$) at the follow-up. In a study by Arnold et al. [42], 79 adults, 65 years of age or older with hip OA were randomly divided into three groups: aquatic exercise and education, aquatic exercise only, and control. It has been described, a significant increase in fall risk factors ($p = 0.038$) for the patients the aquatics and education group, which increased in falls efficacy compared with controls. Moreover, they demonstrated a significant improvement of physical performance, Timed Up and Go Test, and 6-min walk in the aquatics and education group compared with both aquatics and control groups.

3.6.4. Sport

In a study by Brismée et al. [31], 41 adults with knee OA attended a Tai Chi exercise program or an attention activities program. At follow-up, the Tai Chi group presented less overall pain and better WOMAC physical function than the control group ($p = 0.0089$ and 0.0157 , respectively). Moreover, the Tai Chi group had improvements in WOMAC overall, pain subscale and physical function subscale. In a study by Lee et al. [32], 44 patients with knee OA were randomized to a Tai Chi training program or a waiting list control group. The training group reported significant increments in the total SF-36 ($p = 0.010$) and 6-m walking test ($p = 0.005$). Finally, the WOMAC scores in the training group were markedly improved, although the differences were not statistically significant. Tsai et al. [33] studied

the role of Tai Chi to decrease pain and stiffness in elders with knee OA and cognitive impairment, compared with controls. They demonstrated that both groups increased their WOMAC pain score ($p < 0.001$ for Tai Chi group vs. $p = 0.042$ for control group); on the other hand, the WOMAC Physical Function and Stiffness scores improved only in the Tai Chi group ($p = 0.001$ vs. $p = 0.515$ and $p < 0.001$ vs. $p = 0.324$, respectively). For all these scores, the discrepancies between the two groups improved significantly over time. Cheung et al. [34] randomly assigned 36 older women with knee OA to a yoga program or wait-list control. In their study, the differences between treatment and control groups were significant for WOMAC pain ($p = 0.01$) and stiffness scores ($p = 0.02$). An et al. [50] evaluated 22 patients (29 knees) with knee OA after one-year Baduanjin exercise. Compared with their baseline levels before exercise, patients showed significant improvements in WOMAC pain ($p = 0.000$), stiffness ($p = 0.000$) and physical function subscales ($p = 0.003$), SF-36 ($p = 0.005$), and 6-MWT ($p = 0.036$).

3.7. Effect of Intervention

3.7.1. Pain

Almost all the included studies assessed pain through WOMAC pain and KOOS pain scale. The meta-analysis showed no significant pain decrease (SMD 0.33, 95% CI 0.03 to 0.63) and no heterogeneity ($I^2 = 0\%$) when comparing aquatic exercise and land-based exercise (Figure 2). Compared to controls for pain reduction, aquatic exercise presented significant differences (SMD -0.53 , 95% CI -1.25 to 0.19) and high heterogeneity ($I^2 = 91\%$) (Figure 3), land-based exercise demonstrated no significant differences (SMD -0.26 , 95% CI -0.42 to -0.11) and no heterogeneity ($I^2 = 0\%$) (Figure 4), Tai Chi reported significant differences (MD -2.14 , 95% CI -3.11 to -1.18) and moderate heterogeneity ($I^2 = 38\%$) (Figure 5), Yoga had significant differences (MD -1.82 , 95% CI -2.96 to -0.67) without heterogeneity ($I^2 = 0\%$) (Figure 6).

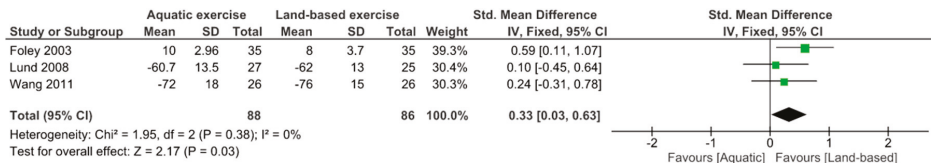


Figure 2. Pain: Aquatic exercise versus Land-based exercise.

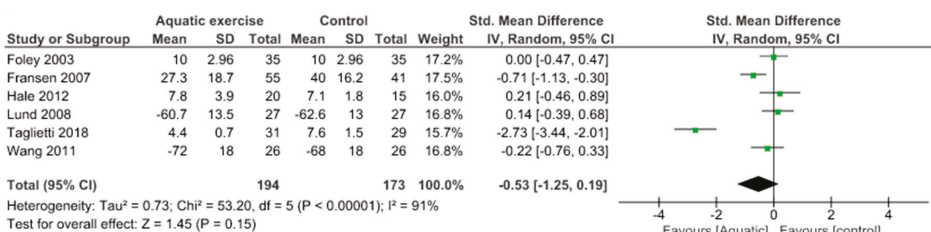


Figure 3. Pain: Aquatic exercise versus Control.

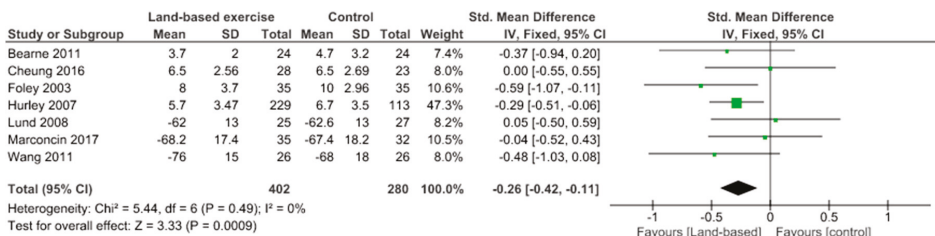


Figure 4. Pain: Land-based exercise versus Control.

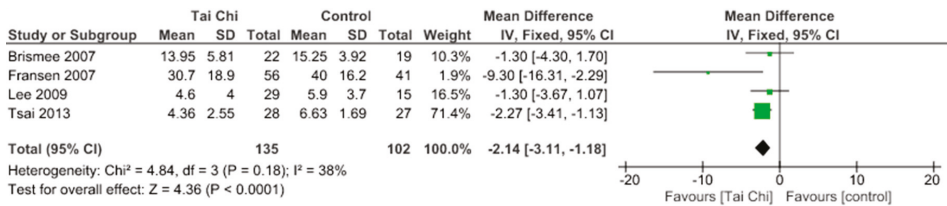


Figure 5. Pain: Tai Chi versus Control.

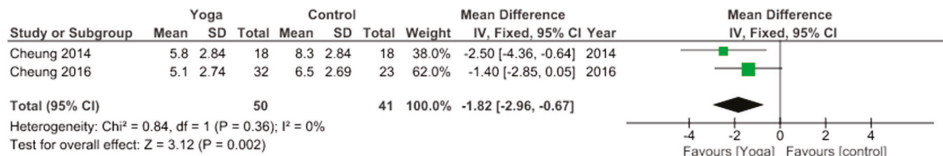


Figure 6. Pain: Yoga versus Control.

3.7.2. Physical Function

Physical function was assessed using the WOMAC physical function scale and KOOS ADL. It has been demonstrated no significant physical function improvements (SMD 0.35, 95% CI 0.05 to 0.65) and no heterogeneity (I² = 0%) between aquatic exercise and land-based exercise (Figure 7). Compared to controls for increase of physical function, aquatic exercise showed significant differences (SMD -0.39, 95% CI -0.62 to -0.16) and no heterogeneity (I² = 0%) (Figure 8), land-based exercise presented significant differences (SMD -0.45, 95% CI -0.74 to -0.17) and high heterogeneity (I² = 57%) (Figure 9), Tai Chi had significant differences (MD -6.80, 95% CI -9.88 to -3.73) and low heterogeneity (I² = 2%) (Figure 10), Yoga reported significant differences (MD -6.07, 95% CI -9.75 to -2.39) without heterogeneity (I² = 0%) (Figure 11).

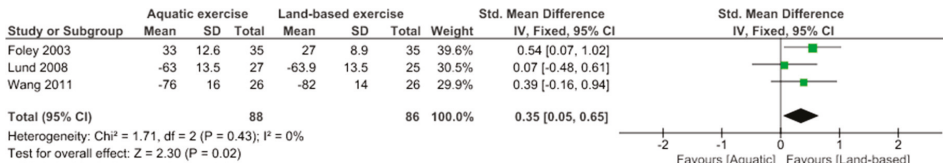


Figure 7. Function: Aquatic exercise versus Land-based exercise.

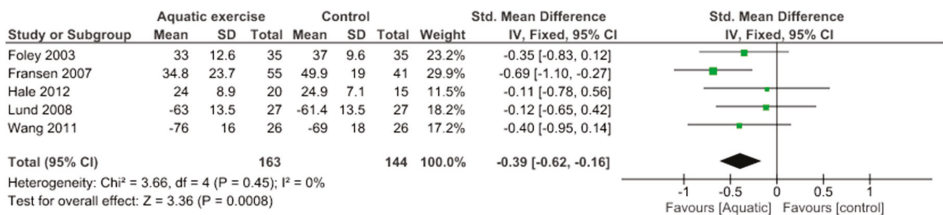


Figure 8. Function: Aquatic exercise versus Control.

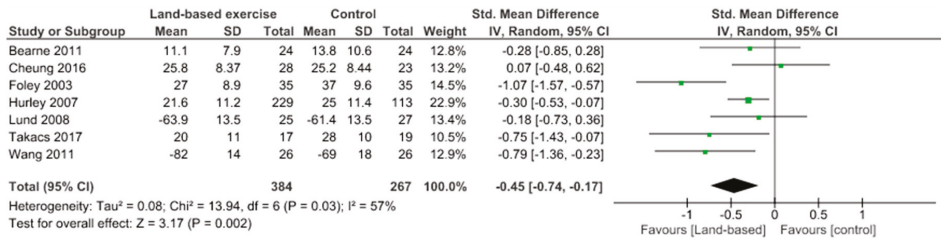


Figure 9. Function: Land-based exercise versus Control.

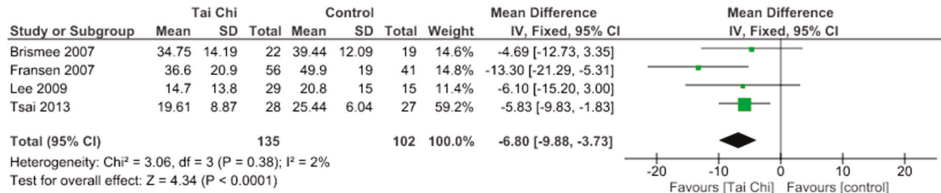


Figure 10. Function: Tai Chi versus Control.

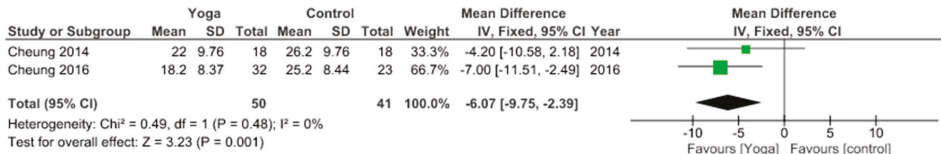


Figure 11. Function: Yoga versus Control.

3.7.3. Quality of Life

Quality of life was evaluated by KOOS QOL and SF-12. The meta-analysis showed no significant improvement in quality of life (SMD -0.20, 95% CI -0.50 to 0.10) and moderate heterogeneity (I² = 54%) in the aquatic exercise compared to land-based exercise (Figure 12). Compared to controls for effect on the quality of life, aquatic exercise produced significant differences (SMD -0.43, 95% CI -0.67 to -0.19) and moderate heterogeneity (I² = 51%) (Figure 13), while land-based exercise reported no significant differences (SMD -0.27, 95% CI -0.54 to -0.01) and no heterogeneity (I² = 0%) (Figure 14).

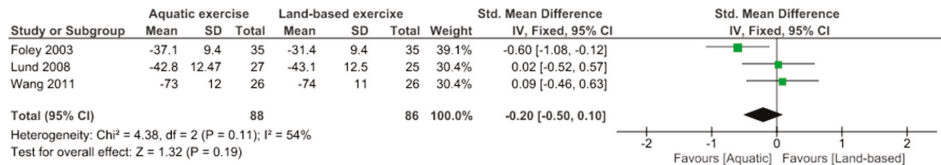


Figure 12. Quality of Life: Aquatic exercise versus Land-based exercise.

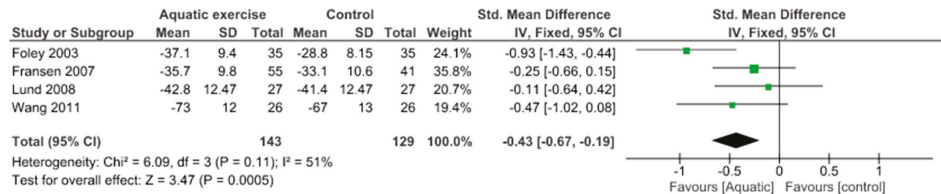


Figure 13. Quality of Life: Aquatic exercise versus Control.

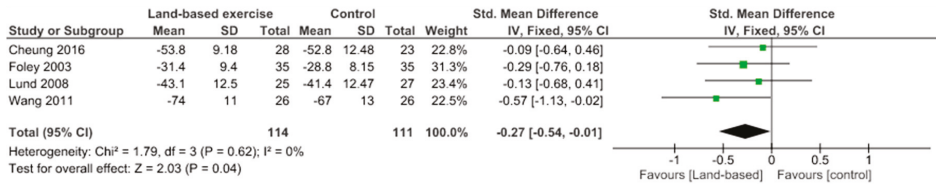


Figure 14. Quality of Life: Land-based exercise versus Control.

3.7.4. Stiffness

Stiffness was checked with the WOMAC stiffness scale. The meta-analysis presented no significant reduction of stiffness (MD 0.16, 95% CI -0.55 to 0.87) and no heterogeneity ($I^2 = 0\%$) in the aquatic exercise compared to the control group (Figure 15). Similarly, in the land-based exercise, there was no significant decrease of stiffness (MD -0.05 , 95% CI -0.66 to 0.56) and no heterogeneity ($I^2 = 0\%$) compared to the controls (Figure 16). Compared to controls improvement of stiffness, Tai Chi showed significant differences (MD -0.74 , 95% CI -1.22 to -0.26) and moderate heterogeneity ($I^2 = 42\%$) (Figure 17), and Yoga reported significant differences (MD -1.06 , 95% CI -1.63 to -0.50) without heterogeneity ($I^2 = 0\%$) (Figure 18).

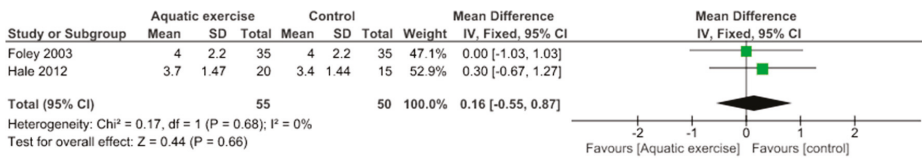


Figure 15. Stiffness: Aquatic exercise versus Control.

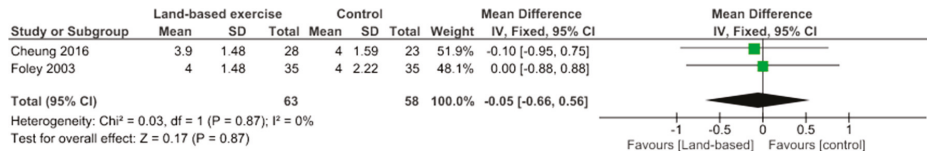


Figure 16. Stiffness: Land-based exercise versus Control.

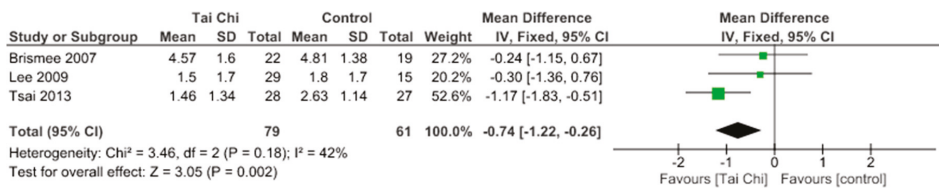


Figure 17. Stiffness: Tai Chi versus Control.

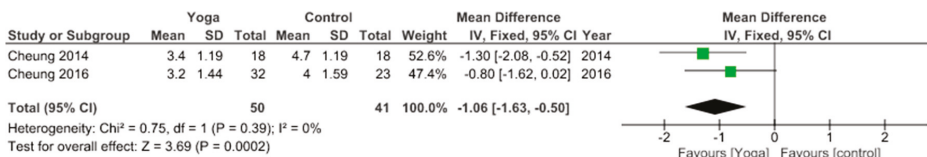


Figure 18. Stiffness: Yoga versus Control.

3.7.5. Dynamic Balance

Only aquatic exercise studies evaluated the dynamic balance by the Time Up and Go test. It has been reported significant improvement of dynamic balance (MD -1.62, 95% CI -1.99 to -1.25) and low heterogeneity ($I^2 = 8\%$) in the aquatic exercise in comparison with controls (Figure 19).

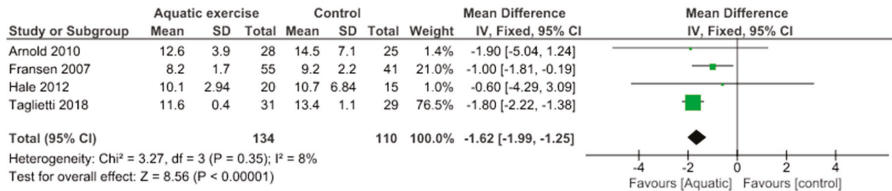


Figure 19. Dynamic Balance: Aquatic exercise versus Control.

3.8. Quality Assessment

The quality of the evidence of the included studies was assessed for 18 comparisons using the GRADE system (Table 5). Of these, 15 comparisons were downgraded by one level due to serious risk of bias, especially as regarded the lack of blinding; therefore, they presented a moderate quality. The remaining three comparisons were downgraded by two levels due to serious risk of bias and inconsistency because there was significant and unexplained variability in results from different trials.

Table 5. GRADE.

Outcomes	Comparisons	n of Participants (Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
Pain	Aquatic vs. Land-based	174 (3 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Function	Aquatic vs. Land-based	174 (3 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Quality of Life	Aquatic vs. Land-based	174 (3 RCT)	serious	serious	not serious	not serious	not serious	⊕⊕⊙⊙ low
Pain	Aquatic vs. Control	367 (6 RCT)	serious	serious	not serious	not serious	not serious	⊕⊕⊙⊙ low
Function	Aquatic vs. Control	307 (5 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Quality of Life	Aquatic vs. Control	272 (4 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Stiffness	Aquatic vs. Control	105 (2 RCT)	serious	serious	not serious	not serious	not serious	⊕⊕⊙⊙ low
Dynamic Balance	Aquatic vs. Control	244 (4 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Pain	Land-based vs. Control	682(7 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Function	Land-based vs. Control	651 (7 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Quality of Life	Land-based vs. Control	225 (4 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Stiffness	Land-based vs. Control	121 (2 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Pain	Tai Chi vs. Control	237 (4 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Function	Tai Chi vs. Control	237 (4 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Stiffness	Tai Chi vs. Control	140 (3 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Pain	Yoga vs. Control	91 (2 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Function	Yoga vs. Control	91 (2 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate
Stiffness	Yoga vs. Control	91 (2 RCT)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊙ moderate

RCT: Randomized Clinical Trial.

4. Discussion

The primary aim of this systematic review and meta-analysis was to summarize the evidence of the efficiency of various types of physical activity on pain, physical function, stiffness, quality of life, and dynamic balance in patients aged 65 or over with knee and hip OA. Another endpoint was to examine either land-based active exercise, aquatic active exercise, and sports, in order to establish greater improvements. Physical activity has shown to be very beneficial for older people with knee and hip OA in terms of pain reduction, better function, performance, and quality of life, with statistically significant improvements compared to the control group. Nevertheless, it was not possible to determine with certainty greater long-term benefits of one type of physical activity compared to the others, also considering the different rates of adherence, and adverse events. The literature review produced almost exclusively RCTs, and this could be justified by the fact that the follow-up was short, and after the follow-up, the control group could have received the same training program as the treatment group. A limitation of this study was represented by the fact that only five studies were composed of three arms, of which two intervention groups and one control group. Three studies (32–34) with two intervention groups presented in the quantitative analysis quite contrasting results about variations in pain and physical function after treatments when comparing land-based with aquatic active exercise; however, showing improvements of both interventions compared to the control group. Also, when comparing Tai Chi or Yoga with aquatic and aerobic exercise [30,35], there were uncertain results on symptom improvement, pain relief, and perceived function. In five studies [44,45,47–49], active exercise represented the only intervention group, and in all of those participants in the study group showed significant improvement in the checked outcomes, such as WOMAC, KOOS, VAS, 6-MWT, and get-up-and-go test. On the other hand, only one study [43] reported no differences between the rehabilitation group and the control group in any outcome measure. When analyzing sports, such as Tai Chi, Yoga, or Baduanjin, all the studies presented significant improvements in pain, physical function, stiffness, and quality of life after the treatment. The quality of the RCTs was determined by the Cochrane Risk of Bias Tool. 18 out of 22 studies presented an unclear or high risk of bias, and it was caused by the inability of blinding personnel and participants when performing physical activity interventions, even more, if control groups underwent no intervention. In fact, the blinding tool of Cochrane Risk of Bias was inadequate or unclear in all the studies selected. Two case series [29,50] were evaluated using the MINORS score. They presented an average score of 11.5 points on a maximum of 24, influenced by the fact that they were non-comparative studies, thus resulting in 0 points in 4 of 12 items. Dong et al. [52] presented no significant difference for pain relief and physical function between aquatic exercise and land-based exercise for patients with knee OA, for both short- and long-term interventions. Goh et al. [53] studied the relative efficacy of different exercises for patients with knee and hip OA. In their systematic review, pain, function, and performance were significantly better with all types of exercise than usual care. Aerobic was the most beneficial exercise for pain and performance, whereas mind-body was also the best for pain and function. Moreover, strengthening and flexibility exercises improved multiple outcomes at a moderate level, while mixed exercise was the least effective for all outcomes, superior only to usual care. Bartels et al. [22] proved that aquatic exercise produced a small short-term advancement compared to no intervention in pain, disability, and quality of life for people with knee or hip OA. In a systematic review and meta-analysis by Lauche et al. [54], participants with knee osteoarthritis training Tai Chi presented an increase of pain, physical function and stiffness with moderate evidence and an increase of quality of life with strong evidence. Cheung et al. [51] demonstrated the effectiveness of yoga to reduce pain, stiffness, and swelling, even if, in their review, the results on physical function were inconclusive because of a variety of outcome measures being used. Another limitation of this review was due to the heterogeneity of the included studies, which presented different scores with various primary and secondary outcomes, different protocols—especially for aquatic and land-based exercise—with distinct types of exercise, different timings of follow-up with variable duration of the single session and the entire program. Therefore, it was not possible to clearly compare the obtained results of the different study groups,

although it was evident the efficacy of every type of physical activity compared to the control groups. Furthermore, adherence to physical activity was reported by 14 of the included studies. In these studies, the adherence to the programs was high, with an attendance of about 80% at the rehabilitation sessions, without significant differences between land-based and aquatic exercise and sport, although that attendance was higher in hydrotherapy when compared with other intervention groups [30,37,38]. The adherence to a physical exercise regimen is essential in order to improve physical performance and function and reduce pain, especially in older patients. Van Gool et al. [55] proved that higher exercise adherence leads to improvements in physical performance and self-reported disability in older adults with knee OA. All the included studies presented the details of dropouts. Twelve studies reported the adverse events that happened over the treatment period. In 4 studies no side effects, complications, or injuries were reported during the physical program [33,34,41,45]. Muscle soreness, increased foot and knee pain, and low back pain after exercise were the most common adverse effect, while they were recorded in a few patients [31,35,36,39,42,49]. Arnold et al. [42] described one moderate adverse effect, that consisted of spinal pain due to a fall. In a study by Fransen et al. [30], 11 participants presented a serious adverse, which were not related to the intervention. Lund et al. reported [38] 11 adverse effects in the land-based group and three adverse effects in the aquatic group ($p = 0.012$).

5. Conclusions

This review and meta-analysis show that all active exercise and sport are an effective conservative treatment for elderly people with OA, in order to improve pain and physical function. The meta-analysis reported no significant differences in improvements in pain, physical function, and QOL between aquatic and land-based exercise. Compared to controls, the aquatic exercise showed significant differences for pain reduction and increase of physical function, quality of life and dynamic balance, land-based exercise presented significant differences for physical function, Tai Chi and Yoga demonstrated significant differences in improvements in pain, physical function, and stiffness. However, the number of studies in this research area is still too few to establish which physical activity leads to better improvement in pain, physical function, stiffness, and quality of life. More high-quality studies with a lower risk of bias are needed in order to support these results, and they should be designed as RCTs comparing aquatic exercise with land-based exercise and sport. Moreover, in future studies aquatic and land-based exercise should be standardized, with the creation of an exercise protocol explaining the program, the frequency and the duration of the exercise's sessions and with the use of similar scores, in order to produce comparable data, to avoid dropouts and to increase the adherence to the programs.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2077-0383/9/4/1167/s1>, Figure S1: PRISMA Checklist.

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Review

The Role of Physical Activity and Rehabilitation Following Hip and Knee Arthroplasty in the Elderly

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Abstract: Hip and knee replacement is an effective treatment for symptomatic, end-stage hip and knee osteoarthritis, aiming to relieve pain and restore joint function. Several postoperative rehabilitation protocols and physical activities are proposed in routine clinical practice. However, their effect on clinical outcome and implant revision in patients undergoing joint replacement is still unclear. A systematic review of the literature was performed through a comprehensive search on online databases including Pubmed-Medline, Cochrane central, and Google scholar. We included all the available studies on postoperative physical activity and rehabilitation protocols after total knee and total hip arthroplasty in patients older than 65 years. The primary endpoint was to evaluate the effect of physical activity and rehabilitation on clinical outcome; the secondary outcome was to determine the effect on patients' quality of life (QoL) and implant survival. Although the heterogeneity of the rehabilitation protocols and outcome measures did not allow to draw definitive conclusions, most studies suggested that aquatic therapy, ergometer cycling, and fast-track protocols have a beneficial effect on muscle strength, gait speed, and main clinical scores after total hip arthroplasty. Similarly, enhanced rehabilitation protocols produced an improvement in primary and secondary outcomes after total knee arthroplasty.

Keywords: hip arthroplasty; knee arthroplasty; elderly; physical activity; rehabilitation; physiotherapy

1. Introduction

Osteoarthritis (OA) is a major cause of disability in elderly patients. The prevalence of hip and knee OA has been growing over the last decades, being around 25% in the population between 65 and 85 years of age [1]. OA has a considerable impact on patients' quality of life (QoL), activities of daily living, and general health status. Due to the large number of patients suffering from this condition and the considerable cost of care, OA represents a significant economic burden for healthcare systems [2].

Joint replacement is the only definitive treatment for symptomatic end-stage hip and knee OA, aiming to relieve the pain and restore joint function. Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are usually followed by an intense rehabilitation program focused on muscle strengthening, stretching, range of motion (ROM) recovery, gait rehabilitation, neuromuscular function, and proprioception recovery.

Nowadays, there is an increasing number of elderly people practicing sports and physical activity, whether low-impact (such as cycling, aquafit, golf, swimming) or medium-/high-impact (skiing, running, tennis, dancing, Nordic walking, etc.). Often, patients undergoing hip and knee arthroplasty

aim to return to their previous activity level. However, the effect of such activities on the clinical outcome and survival of the implant is still unclear.

Numerous postoperative interventions have been studied, including in-hospital rehabilitation, inpatient rehabilitation, home exercises, tele-rehabilitation, aquatic therapy, and fast-track protocols, but it is still unclear which of these interventions is the most effective following hip and knee arthroplasty in order to achieve a complete functional recovery. Moreover, there is poor evidence about what type of physical activity can be allowed or encouraged without affecting implant survival.

The primary endpoint of this systematic review was to evaluate the impact of physical activity and rehabilitation on clinical objective and subjective outcomes, after TKA and THA. The secondary outcome was to establish the effect of these activities on patients' QoL and on implant revision rates.

2. Materials and Methods

The present systematic review was performed in accordance to the PRISMA guidelines [3] and followed the Cochrane methodology for systematic reviews [4]. The MINORS (methodological index for non-randomized studies) score was used to assess the methodological quality of non-randomized studies [5].

2.1. Primary Outcomes

The primary endpoint was to assess the effect of physical activity and rehabilitation on clinical outcome, measured by validated joint-specific objective and subjective clinical measurements. When reported, the considered outcome measures for THA were the WOMAC (Western Ontario and Mc Master University) index, hip abductor strength, Harris Hip Score (HHS), gait speed, UCLA score, Lequesne Hip/Knee score. The considered outcome measures for TKA were the WOMAC index, Lequesne Hip/Knee score, 10 min walking test, walking speed, stair ascending time, knee extensor and flexor power, thigh muscle cross-sectional area, 6 min walking test (6MWT), Knee Society score (KSS), range of motion (ROM), modified gait efficacy scale (mGES), timed up and go (TUG).

2.2. Secondary Outcomes

The secondary endpoint was to assess the effect of physical activity and rehabilitation on implant revision rates and self-reported quality of life, using questionnaires.

2.3. Search Methods for Identification of the Studies

Online databases, including Pubmed-Medline and Google Scholar, were searched for relevant articles. The search string used was the following: ("sports"(MeSH Terms) OR "sports"(All Fields) OR "sport"(All Fields)) AND ("exercise"(MeSH Terms) OR "exercise"(All Fields) OR ("physical"(All Fields) AND "activity"(All Fields)) OR "physical activity"(All Fields)) AND after(All Fields) AND ("arthroplasty"(MeSH Terms) OR "arthroplasty"(All Fields)) AND ("aged"(MeSH Terms) OR "aged"(All Fields) OR "elderly"(All Fields)).

The studies retrieved were firstly screened by title, and if relevant, the whole abstract was read. After a first selection and exclusion of nonrelevant papers, the full text of the potentially eligible articles was retrieved and read by two reviewers, for possible inclusion. Discordant opinions were solved through the consultation of a third reviewer. After the electronic search was completed, the bibliography of the included relevant articles was screened manually to identify further papers, potentially missed in the electronic search. The search process is summarized in the flow diagram in Figure 1.

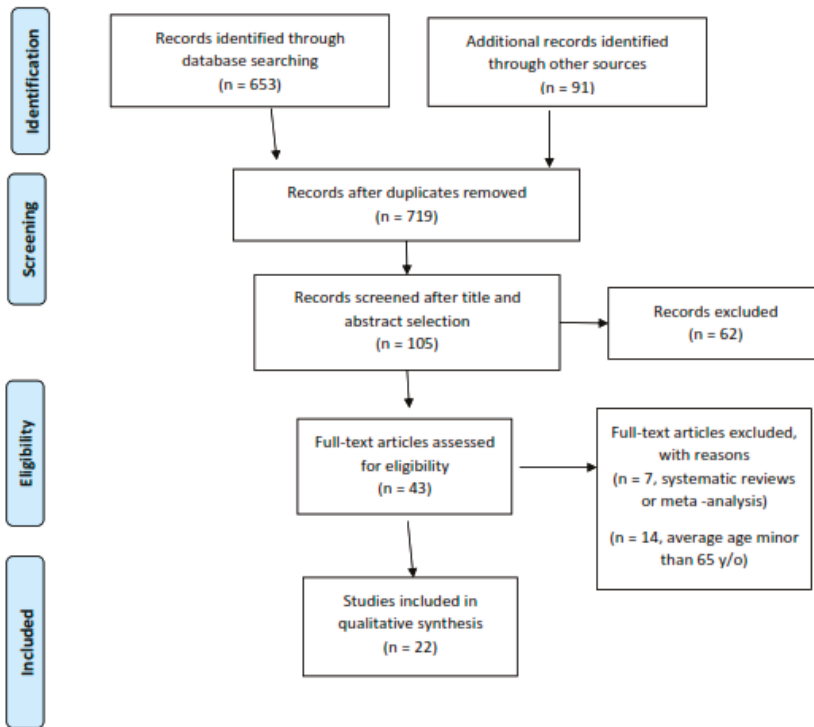


Figure 1. Flow chart of the study inclusion process.

2.4. Inclusion and Exclusion Criteria

The studies considered for inclusion were randomized controlled trials (RCT), prospective cohort studies (PCS), retrospective and prospective case–control studies (CCS), longitudinal studies (LS), and cross-sectional studies (CSS). Case reports, reviews, and meta-analyses were excluded. Studies had to report on the postoperative physical activity (intended as early and late physiotherapy, aquatic therapy, and sport activity) in elderly patients who underwent THA and/or TKA. According to the definition of elderly of the WHO, only studies where the average age of the cohorts was superior to 65 years were considered. Studies reporting on both THA and TKA patients needed to present the results of the two groups separately.

2.5. Data Collection and Analysis

Data were extracted from the included articles, according to the primary and secondary outcomes considered for the aim of this review. After extraction, generic data concerning the paper were reported in Table 1. For an appropriate presentation of the data, the results were divided on the basis of the type of surgery (TKA or THA).

Table 1. Details of the included studies.

Study	Type of study, Level of Evidence	Number of Patients	Mean Age (y)	Type of Surgery	Type of Physiotherapy–Exercise–Sport Activity
Gschwend N. et al. Acta Orthop Scand. 2000 [6]	Retrospective clinical study–LOE III	100	65 GROUP A 65 GROUP B	THA	Group A: alpine/cross-country skiing, summer sports (trekking, biking, swimming) Group B: no winter sports
Lavernia CJ et al., J Arthroplasty 2001 [7]	Retrospective	28	68 at the time of surgery	TKA	Physical activity level assessed with UCLA activity score and Charnley class
Jones DL et al. J Rheumatol. 2004 [8]	CCS–LOE III	52	cases 70.5 controls 75	TKA	Leisure and occupational historical/high-intensity activity, measured as MET (metabolic equivalent of task) -hours/wk
Mont MA et al. J Arthroplasty. 2008 [9]	Retrospective CCS–LOE III	148	High-impact cohort: 66 High-activity cohort: 69 Sedentary cohort: 71	TKA	High-activity: baseball and basketball, gymnastics, hockey; High-impact: aerobics, ice/roller skating, jogging, martial arts, racquetball/squash, rock climbing, skiing (downhill), soccer, tennis (singles)
Giaquinto S et al. Arch Gerontol Geriatr. 2010 [10]	RCT–LOE I	64	Group A: 70.6 Group B: 70.1	THA	Group A: conventional gyms (no-hydrotherapy group) Group B: hydrotherapy group
Giaquinto S et al. Arch Gerontol Geriatr. 2010 [11]	RCT–LOE I	58	Geriatric population, groups matched by age, gender, and body mass index (BMI)	TKA	Group A: conventional gym treatment Group B: hydrotherapy
Liebs TR et al. J Bone Joint Surg Am. 2010 [12]	RCT–LOE I	203 THA 159 TKA	THA Group A: 67.2; Group B 67.2 TKA Group A: 69.9; Group B 69.7	TKA and THA	Group A: No ergometer cycling Group B: ergometer cycling
Liebs TR et al., Arch Phys Med Rehabil. 2012 [13]	RCT–LOE I	280 THA 185 TKA	THA Group A: 66.7; Group B 69.1 TKA Group A: 68.5; Group B 70.9	TKA and THA	Group A: aquatic therapy (pool exercises aimed at training of proprioception, coordination, and strengthening) from the 6th day after surgery Group B: aquatic therapy from the 14th day after surgery
Mayr HO et al., J Arthroplasty. 2015 [14]	Retrospective CCS–LOE III	81	71.8 ± 5.4	TKA	High-impact: alpine skiing, rock climbing, dancing, tennis; Medium-impact: hiking, cross-country skiing, Nordic walking, fitness; Low-impact: aqua fit, golf, cycling, swimming

Table 1. Contd.

Study	Type of study, Level of Evidence	Number of Patients	Mean Age (y)	Type of Surgery	Type of Physiotherapy–Exercise–Sport Activity
Winther SB et al. Acta Orthop. 2015 [15]	Retrospective cohort study–LOE III	585 THA 335 TKA	65–66 for THA/TKA primary surgery, 68/67 for revision surgery	TKA and THA	Fast-track (treatment chain)
Heiberg KE et al., Arthritis Care Res. 2016 [16]	RCT–LOE I	60	Training group 70.2 Control group 70.6	THA	Case group: walking skill training program 3–5 months after surgery Control group: usual training
Paxton EW et al., Acta Orthop. 2016 [17]	Prospective comparative study–LOE II	5,678 THA; 11,084 TKA	THA: 68 TKA: 67	THA and TKA	Self-reported minutes of physical activity/week
Taniguchi M et al., J Arthroplasty. 2016 [18]	PCS–LOE II	81	72.1	TKA	Passive knee range of motion (ROM) exercises, strengthening, gait and ADL (activities of daily living) training, cycling with a stationary bicycle
Hiyama Y et al., J Knee Surg. 2017 [19]	Prospective cohort study–LOE II	59	71.7	TKA	standardized rehabilitation program, targeting knee range of motion, pain control, and quadriceps strength
Mitrovic D et al., Clin Rehabil. 2017 [20]	RCT–LOE I	70	Study group: 69.2 Control group: 68.1	THA	Supplementary arm and upper body exercise program to be compared with the standard-rehabilitation program group (upper limb flexibility, range of motion, and muscle strength, along with regular, deep breathing exercises)
Valle C et al., Sportverletz Sportschaden Organ Ges Orthopädisch-Traumatol Sportmed. 2017 [21]	Retrospective CCS–LOE III	130	69.2	TKA	Sport group: trekking, swimming, golf, Nordic walking, skiing No-sport group: without any sport activity
Mikkelsen LR et al., Physiother Res Int J Res Clin Phys Ther. 2012 [22]	RCT–LOE I	44	Intervention group 67.7 Control group 66.8	THA	Fast-track group: rubber band resistance (Thera-Band) and step exercises. Address the muscle groups mostly affected after THA Control group: standard rehabilitation consisting of exercises without external resistance and progression
Rahmann AE et al., Arch Phys Med Rehabil. 2009 [23]	RCT–LOE I	65	Group 1: 70.4 Group 2: 69.4 Group 3: 69	TKA and THA	Group 1: ward physiotherapy treatment each day, following the standard orthopedic clinical pathway; Group 2: aquatic physiotherapy program (30% body weight (BW)); Group 3: water exercise program (10%BW).

Table 1. Cont.

Study	Type of study, Level of Evidence	Number of Patients	Mean Age (y)	Type of Surgery	Type of Physiotherapy–Exercise–Sport Activity
Moffet H et al., Arch Phys Med Rehabil. 2004 [24]	RCT–LOE I	77	Standard physiotherapy 68.7 Intensive physiotherapy 66.7	TKA	STANDARD: simple exercises to retrain lower-limb strength (quadriceps, hamstrings, hip abductors, and extensors) and to increase knee mobility, as well as some advice about knee positioning, ice application, and gait retraining; INTENSIVE: 5 components: warm-up, specific strengthening exercises, functional task-oriented exercises, endurance exercises, and cool-down
Valtonen A et al., Arch Phys Med Rehabil. 2010 [25]	RCT–LOE I	50	Training Group 66.2 Control Group 65.7	TKA	Training group: 12-week progressive aquatic resistance training; Control: no intervention
Valtonen A et al., Arch Phys Med Rehabil. 2011 [26]	RCT–LOE I Follow up	42	Training Group 66.2 Control Group 65.7	TKA	Training group: 12-week progressive aquatic resistance training; Control: no intervention
Bauman S et al., Clin J Sport Med. 2007 [27]	Retrospective case series–LOE IV	170 THA 184 TKA	THA 66.4 TKA 68.9	TKA and THA	Physical activity assessed by UCLA activity score

TKA: total knee arthroplasty, THA: total hip arthroplasty, LOE: Level of evidence, CCS: case-control studies, RCT: randomized controlled trials, PCS: prospective cohort studies.

2.6. Risk of Bias Assessment

Given the heterogeneity of the included studies, two different critical appraisal tools were used. For randomized clinical trials, the Cochrane risk of bias assessment tool was applied, providing a grade of risk (low and high risk) of bias for the index study in five elements of the study design (sequence generation, allocation concealment, blinding, incomplete data addressment, and selective reporting). The MINORS score was used for non-randomized studies.

3. Results

3.1. Results of the Search

From the electronic and manual search, a total of 744 papers were identified. After the selection process, 43 papers were considered eligible to be included in the study. Fourteen papers were excluded because the average age of the cohort was below 65 years; 7 further papers were excluded for being reviews or meta-analyses. Twenty-two papers (11 RCT, 3 PCS, 6 retrospective CCS, one retrospective CS) were eventually included in the study (Figure 1).

The results of risk of bias assessment are presented in Appendices A and B.

The included studies reported data on a total of 20,139 patients: 12,818 underwent TKA, while 7321 underwent THA. The average age ranged from 65 to 72.1 years.

3.2. Total Hip Arthroplasty

Six studies reported the results of THA alone and five studies the results of both THA and TKA. Seven studies were RCT, two were retrospective CCS, one was a PCS, and one was a retrospective case series.

The risk of bias assessment revealed that six of the seven RCT had one or more major methodology flaws, therefore the risk of bias within a single trial was present for these studies (Appendix A). Among non-randomized studies, some showed major limitations, especially concerning patient allocation, blinding, and data collection. The mean MINORS score was 13, indicating a moderate risk of bias (Appendix B). Only one study specified the surgical approach (posterior) [16].

The most frequent primary outcome reported was the WOMAC index, mentioned in four papers [7–10]. All the included studies showed an improvement in the three subscales (function, pain, and stiffness), with mean values of 13.7, 9.3, and 18.5, respectively. Different types of physical activity and physiotherapy (early and late hydrotherapy [10,13], ergometer cycling [12], intensive physiotherapy addressing specific muscle groups [22]) had a beneficial effect after THA, as measured by the WOMAC score.

Other studies reported heterogeneous patient-related outcome measures and physical test measures. An improvement in Hip disability and Osteoarthritis Outcome Score – Physical Function Shortform (HOOS-PS) was reported by Winther et al. [15] and by Heiberg et al. [16], after an intensive fast-track treatment and after a walking skill training program, respectively. Two papers reported an increase in HHS values [11,12]. Regarding the physical tests, improvements in hip abductor strength, gait speed, one-legged stance, and 6MWT were reported after intensive aquatic therapy [23] and fast-track gym treatment [22].

Considering the effect of physical activity on quality of life, three papers reported a significant increase of it using the SF-36 questionnaire (mean value 55.6 three months after surgery) [12,13,20]; other authors reported an improvement using the health-related (HR)QoL and EQ-5D questionnaires after fast-track intensive treatment [15,22]. Poor evidence is available about the effect of physical activity on revision rates: Gschwend et al. reported an inferior rate of implant loosening and revisions in active patients [6], while Bauman et al. reported no signs of wear or loosening in patients with high UCLA score 40 months after surgery [27].

The included studies reported on a vast and heterogeneous group of postoperative activities, ranging from high- and low-impact sport activity, to enhanced physiotherapeutic protocols and early and

late hydrotherapy (Table 2). Aquatic therapy, fast-track treatment and leisure physical activity were the most frequently reported activities.

Table 2. Types of activity and number of studies in which they were reported.

TYPE OF ACTIVITIES	THA (n° of studies)	TKA (n° of studies)
Hydrotherapy	3 [1–3]	5 [2–6]
Ergometer cycling	1 [7]	2 [7,8]
Intensive physiotherapy		3 [8–10]
Fast-track treatment	2 [11,12]	1 [11]
Walking skill training	1 [13]	
Arm/upper body exercise	1 [14]	
Leisure activity (MET-hours/week, minutes/week)	2 [15,16]	4 [15–18]
Winter sports (alpine skiing, cross-country skiing)	1 [19]	3 [18,20,21]
Summer sports (trekking, hiking, biking, swimming)	1 [19]	3 [18,20,21]
High-impact physical activity (baseball, gymnastics, hockey, basketball, martial arts, football, tennis)		2 [18,20]
Low-impact physical activity (aquafit, golf, cycling, swimming)		2 [18,20]

3.3. Total Knee Arthroplasty

Nine studies reported the effect of physical activities on TKA alone, and five on both THA and TKA. Out of these, six were RCT, four were retrospective CCS, three were PCS, and one was a retrospective case series. The risk of bias assessment showed that three of the six RCT had one or more major methodological flaws, therefore the risk of bias within a single trial was present for these studies (Appendix A). Among non-randomized studies, some also showed major limitations, especially concerning patient allocation, blinding, and data collection. The mean MINORS score for TKA studies was 13.4, indicating a moderate risk of bias (Appendix B).

Similar to THA, the most frequently reported measure of primary outcome was the WOMAC index, mentioned by six studies [11–14,24,25]. Differently from the data presented on THA, only four of six studies showed an improvement in the WOMAC index. Only in two of these, the difference was statistically significant. The study by Liebs et al. did not corroborate the use of a cycloergometer after TKA [12]. An early start of hydrotherapy after TKA led to an improved WOMAC at three and six months of follow-up [11,13], but after one year the difference with respect to the control groups disappeared [13,25,26]. In a retrospective CCS by Mayr et al., a significant correlation between sport activity level (high-, medium-, and low-impact) and WOMAC index was reported.

Other patient-related outcome measures analyzed in the reported studies were the Knee injury and Osteoarthritis Outcome Score (KOOS) – Physical Function Shortform (KOOS-PS), KSS, Lequesne Hip/Knee score, and Oxford Knee Score (OKS). An improvement in KSS, KOOS, and OKS was reported after fast-track treatment [15] in patients performing high-activity and high-impact sports [9,14] (though no difference was shown in clinical outcome between these subgroups) [21], after a rehabilitation program targeting quadriceps strength and range of motion [19], and in patients accomplishing moderate-to-high physical activity (UCLA > 6) [27]. Moreover, a wide range of physical tests were reported, including the 6MWT, TUG, sit-to-stand time, knee flexor and extensor power, mGES, gait speed, and thigh muscle cross-sectional area. Aquatic therapy, gait training, muscular strengthening, and enhanced rehabilitation programs had a beneficial effect on these parameters [18,19,24,25], even at long-term follow-up [20].

Considering the effect of physical activity on quality of life, ergometer cycling did not produce significant improvement evaluated with the SF-36 questionnaire [12]. In contrast, early-phase aquatic

therapy, enhanced physiotherapeutic protocols, and fast-track treatment induced beneficial effects according to the SF-36 and EQ-5D questionnaires [9,11,18,21].

Considering revision rates and prosthetic wear or loosening, Jones et al. showed that leisure, occupational, and high-intensity activity, measured as MET-hours/week, did increase the risk for revision [8]. Mont et al. reported that high-impact and high-activity sports are not a cause of implant failure (considering clinical and radiographical criteria of the Knee Society rating system), at 4 years of mean follow-up [9]. Similarly, Mayr et al. reported no evidence of wear or loosening, as well as similar revision rates, in patients performing high-impact activity vs. those performing medium- or low- impact activities [14]. Finally, comparing a sportive patient group with an inactive patient group, Valle et al. showed a reduced revision rate in the sport group (15.2% vs. 23.8%) at 12 years of follow-up [25].

4. Discussion

THA and TKA are extremely common surgical procedures. However, there is no consensus about the most effective postoperative physiotherapy and physical activities allowing an optimal recovery. The aim of this systematic review was to analyze the current evidence on the role of physical activity and rehabilitation in patients' clinical outcome after hip and knee arthroplasty.

Aquatic therapy resulted beneficial after THA, with improvements in terms of muscle strength, gait speed, main clinical scores (WOMAC, Lequesne Hip/Knee score, HOOS, HHS), patient satisfaction, and QoL (SF-36, EQ-5D questionnaires). However, an early start of hydrotherapy (6 vs. 14 days after surgery) did not produce further advantages [10,13,23]. Both ergometer cycling and intensified exercise programs resulted beneficial in terms of patient QoL, maximal gait speed, hip abductor muscle strength, and WOMAC index [12]. Interestingly, a supplementary arm and upper body exercise program produced a significant improvement in functional abilities [20]. In general, all protocol focusing on intensified exercises and additional activities and the practice of an adequate sport activity produced a beneficial effect on early and late postoperative recovery and limb function. However, it is unclear whether the same advantages are relevant in term of durability of the prosthetic implant, though it has been reported that a moderate or active lifestyle do not affect implant survival [14,15,26]. Nonetheless, more than 50% of patients undergoing total joint arthroplasty (TJA) do not respect the physical activity guidelines, suggesting that patient education should be improved [17].

It has been demonstrated that fast-track THA protocols are effective in terms of reduced length of stay, patient satisfaction and function [15,28]. However, fast-track is a complex approach, requiring patient preoperative optimization, anesthesia management, systemic pain treatment (nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, short-acting opioids), early mobilization, and physiotherapy [11,27–30]. It can be really challenging to set up this process in some institutions or for patients with severe comorbidities [31].

Aquatic therapy produced a beneficial effect on the clinical outcome after TKA. The WOMAC index improved in four out of six studies, similarly to SF-36 score, Lequesne Hip/Knee score, and patient satisfaction score [9,13,16,19,20]. Furthermore, also the use of early hydrotherapy (6 days after surgery) showed a beneficial effect similar to the use of NSAIDs [8]. Aquatic therapy improved quadriceps strength, walking speed, stair ascending time. The results of the cycle ergometer are controversial, and this practice is not supported for TKA recovery [12]. It has been suggested that ergometer cycling produces an improvement in strength and proprioception after TKA but that the overload on the knee may induce soft tissue edema and joint effusion, jeopardizing the positive effects [12].

In general, enhanced rehabilitation protocols and fast-track surgery after TKA produced an improvement in primary and secondary outcomes, thus indicating that an early recovery of muscular function and joint proprioception is essential.

The practice of high-impact and high-activity sports is often discouraged by surgeons because of the risk of mobilization and wear of implants' components. However, the current evidence shows that this practice leads to improved clinical outcomes in elderly patients in term of ROM, KOOS scores,

WOMAC index, KSS, pain, and rate of revision [9,14]. Several authors reported that physical activity does not increase the risk of revision. One study suggested that moderate sport activity can improve osteointegration, with a decrease in osteolytic changes and prosthetic loosening [21]. On the basis of these findings, orthopedic surgeons should recommend exercising and participation in moderate and high-level sport activities after joint replacement. However, these data are limited, and there is a need for well-designed studies to draw definitive conclusions on these aspects.

This review has some limitations. First of all, the heterogeneity of the postoperative rehabilitation protocols and activities and the variety of outcome measures reported do not allow to pool the results and perform a statistical analysis. In addition, only one study reported about the surgical technique used and operation details. Nowadays, there are several surgical approaches and different implants that can significantly influence patients' recovery. However, there is scarce evidence suggesting consistent advantages of one technique over the others on medium- to long-term outcome.

To limit the risk of bias, all papers were evaluated through Cochrane Risk of Bias Assessment and MINORS score, thus enlightening how all RCT were well structured, showing only some incongruity in allocation concealment and blinding. Nevertheless, this seemed not to compromise the quality and the relevance of the results.

5. Conclusions

Although the heterogeneity of the rehabilitation protocols and outcome measures do not allow to draw definitive conclusions, most studies suggest that patients over 65 years of age benefit from enhanced physiotherapy protocols, aquatic therapy, and physical activity after knee and hip arthroplasty. The effect of physical activity on implant revision rate and survival remains controversial.

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Appendix A. Cochrane Risk of Bias Assessment. Low risk (L), High risk (H), Unclear (U)

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Data Addressed	Free of Selective Reporting	Free of Other Bias
Giaquinto et al. [7]	U	L	U	L	L	L
Giaquinto et al. [16]	L	L	L	L	L	L
Liebs et al. [8]	L	L	H	L	L	L
Liebs et al. [9]	L	L	L	L	L	L
Heiberg et al. [6]	H	H	L	L	L	H
Mitrovic et al. [12]	L	L	L	L	L	L
Mikkelsen et al. [10]	U	U	H	U	L	H
Rahmann et al. [13]	L	L	L	L	L	H
Moffet et al. [24]	L	L	L	L	L	L
Valtonen et al. [25]	U	L	H	L	L	L

Appendix B. MINORS score. The Ideal Scores for Non-Randomized Studies are 16 for Non-Comparative Studies and 24 for Comparative Studies

Study	SCORE
Gschwend et al. [6]	19
Jones et al. [8]	20
Mont et al. [9]	12
Mayr et al. [14]	17
Winther et al. [11]	11
Paxton et al. [17]	12
Taniguchi et al. [18]	15
Hiyama et al. [19]	15
Valle et al. [21]	11
Valtonen et al. [26]	11
Bauman et al. [15]	10

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Review

Return to Sport Activity in the Elderly Patients after Unicompartmental Knee Arthroplasty: A Systematic Review and Meta-Analysis

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Abstract: In patients with knee osteoarthritis, when only medial or lateral compartment of the knee is involved, unicompartmental knee arthroplasty (UKA) is a reliable option for addressing the symptoms and restore function. The main aim of the present review is to systematically collect the available evidence concerning the return to sport activity in the elderly patients after UKA. An electronic search was carried out on the following databases; Pubmed-Medline, Cochrane central, and Scopus, searching for randomized controlled trials, prospective cohort studies, retrospective case-control studies, and case series. Data concerning the evaluation of the return to sport (RTS) and of functional outcomes in the elderly patients after UKA surgery. MINORS score was used to assess the risk of methodological biases. Odds ratios and raw proportions were used to report the pooled effect of UKA on the return to sport in comparative and non-comparative studies, respectively. Same level RTS in elderly patients was of 86% (pooled return proportion 0.86, 95%CI 0.78, 0.94), showing also better relative RTS and time to RTS of patients undergoing UKA, in comparison to those undergoing TKA. Sport-specific RTS showed that higher return rates were observed for low-impact sports, whereas high-impact sports prevented a full return to activities. UKA is a valid and reliable option for elderly patients to satisfactorily resume their sport practice, especially for low impact activities. The rate of return to sports following UKA is higher than TKA.

Keywords: knee osteoarthritis; unicompartmental knee arthroplasty; sport; activity; elderly

1. Introduction

In the present social scenario, the needs of elderly people are changing. It is not infrequent that patients want to stay active and be able to perform physical exercises and sport activities even in an advanced age [1,2]. However, these requests are often undermined by chronic painful conditions, such as osteoarthritis (OA), that do not allow the patient perform all desired activities [3]. In particular, knee OA is a common, debilitating condition that is increasingly widespread accordingly with the aging of the general population [1,2,4–6]. It is widely accepted that the definitive treatment for the end stage knee OA is the joint arthroplasty [7]. When only medial or lateral compartment of the knee is involved, unicompartmental knee arthroplasty (UKA) is a reliable option that is raising in popularity [8,9]. Indications to UKA have been widely discussed, but it is well known that this implant provides some advantages: lower invasiveness, shorter rehabilitation time, restoration of a wider

range of motion, and physiological proprioception of the knee due to cruciate ligaments retention [10]. Several studies in literature reported the benefits of patients who underwent UKA in terms of pain relief and quality of life, with a good to excellent return to activities [11]. The opportunity to move and walk without pain, with also a good recovery of the motion, allows individuals to perform physical activity and sport, which is particularly important to prevent systemic diseases associated to sedentary life such as obesity, diabetes, cardiovascular accidents, and cancer [12–14]. One of the principal expectation for active patients before undergoing UKA surgery, is about their chances to perform physical activity and sport after surgery. Moreover, active patient is mostly interested in type and level of sport activity [15,16]. The current scientific literature answers those questions mainly with recommendations based on expert opinions and surgical society guidelines [17,18], but still lacks high level evidence-based guidelines, especially regarding the elderly population. The main aim of the present manuscript is therefore to systematically collect the available evidence concerning the return to sport activity in the elderly patients after UKA, with a special concern to the type of activity. A secondary endpoint of this investigation is to assess the functional outcomes in the same population.

2. Methods

A systematic review and meta-analysis was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [19]. The review was planned and conducted following the PRISMA checklist. According to PICO, the following elements have been used to frame the study question.

Population: Elderly patients.

Intervention: Unicompartmental Knee Arthroplasty (UKA).

Comparison: Total Knee Arthroplasty (TKA) or no comparison.

Outcomes: Return to sport activity and functional outcomes.

2.1. Criteria for Considering Studies for This Review

The studies considered for inclusion were randomized controlled trials (CRT), prospective cohort studies (PCS), retrospective case–control studies (RCS), and case series (CS). The main topic of the papers had to be the evaluation of the return to sport activity and of functional outcomes in the elderly patients after UKA surgery. Case Reports, Reviews, and Meta-analyses were not eligible for inclusion. Moreover, *in vitro* studies and cadaver studies were excluded from the review analysis. Given the specific focus on a selected population, only studies reporting outcomes of patients aged 65 or older were considered for inclusion (average population age > 65).

2.2. Primary Outcome Measures

The absolute numbers and proportions of patients returned to same level sport activities (RTS) was considered as the primary outcome measure and assessed throughout the included studies. Sport-specific return was extracted from the studies, to stratify results according to the type of activities.

2.3. Secondary Outcome Measures

The secondary endpoint was achieved by evaluating the following measures; Oxford Knee Score (OKS), Knee injury and Osteoarthritis Outcome Score (KOOS), Knee Society Score (KSS) and American Knee Society Score (AKSS), University of California Los Angeles (UCLA), Tegner and Lysholm scales, and the Western Ontario McMaster universities osteoarthritis index (WOMAC). These measures were evaluated across the included studies.

2.4. Search Strategy for Study Identification

The online search was carried out on the following databases; Pubmed-Medline, Cochrane central, and Scopus. The following search string was used; (Arthroplasty, Replacement [MeSH Terms])

AND joint, knee [MeSH Terms]) AND sports [MeSH Terms] and (arthroplasties, knee replacement [MeSH Terms]) AND sports [MeSH Terms]. The bibliography of the included studies and of recent review articles was screened for further relevant articles, potentially missed at the electronic search. After duplicates removal, all the retrieved studies were firstly screened by title to find studies dealing with UKA. Two independent reviewers (B.Z. and G.T.) evaluated the abstract of each of the papers considered for inclusion. Discordant opinions concerning study inclusion were discussed with a third experienced reviewer (R.P.). If abstract was not sufficient to define inclusion of a paper, the full-text was retrieved and evaluated. Articles included for review process were retrieved in full-text and read. The search process was summarized in Figure 1.

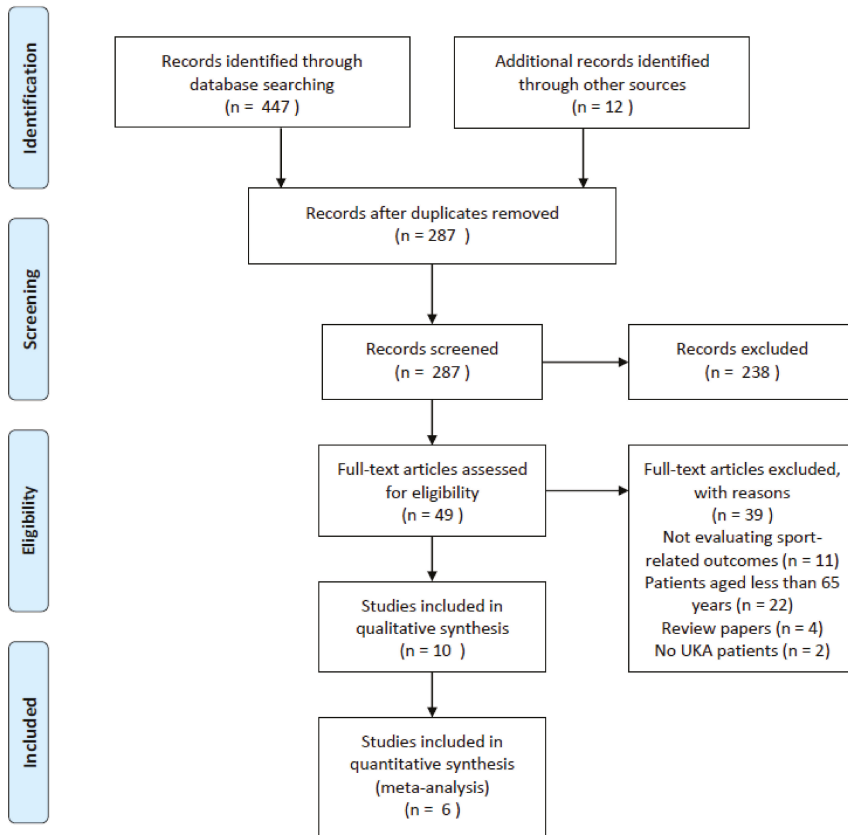


Figure 1. Study selection flowchart (UKA: Unicompartmental Knee Arthroplasty).

2.5. Data Collection and Analysis

Data were extracted independently by two reviewers (B.Z. and L.A.D.B.) and tabulated according to primary and secondary outcomes of this review. Discordant opinions in data extraction were solved by discussion with a third reviewer (R.P.).

2.6. Risk of Bias Assessment

The quality of the included non-randomized studies was independently evaluated by two reviewers (L.D.B. and B.Z.) using the Methodological Index for Non-randomized Studies (MINORS) score. [20] The following domains were assessed; a clearly stated purpose, inclusion of consecutive subjects,

prospective data collection, endpoints appropriate to the purpose of the study, unbiased assessment of the study endpoints, follow-up period appropriate for the study, loss to follow-up of less than 5%, prospective calculation of the study size, adequate control group, contemporary group, baseline group equivalence, and adequate statistical analysis. The last four items are specific to comparative studies. Each item was scored from 0 to 2 points, with a global ideal score of 16 points for non-comparative studies and 24 points for comparative studies.

2.7. Quantitative Analysis

Meta-analysis was carried out to investigate the effect of UKA on the return to sport activity either in comparison with TKA or in non-comparative studies. Furthermore, return to specific sport activities was pooled if at least three studies reported the same sport. Odds ratios (ORs) and raw, i.e. untransformed, proportions were used to report the pooled effect of UKA on the return to sport probabilities in comparative (vs. TKA) and non-comparative studies, respectively. Heterogeneity was evaluated using Q statistic, expressed as the p value for the χ test under the null hypothesis that the between-study variance (τ) equals 0, and I2 test. All the conducted meta-analyses evidenced the presence of significant heterogeneity, defined as a I2 > 55% and/or a Q statistic p value below 0.05. Accordingly, random effect models were applied. Finally, the likelihood of methodological bias among included studies was estimated with the visual inspection of the funnel plot. Analyses were conducted using metafor and meta packages in R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Research Results

Electronic search identified 447 papers, and of these 287 scientific products were screened for analysis. Full text of 49 papers was accurately analyzed and 28 were excluded for following reasons; absence of postoperative sport-related outcomes, cohort mean age lower than 65 years old, duplicated papers and no UKA patients. Finally, 10 [10,21–29] articles were included according PRISMA selection process (Figure 1).

3.2. Included and Excluded Studies

Among 10 studies, only 2 study were prospective [24,26], 6 evaluated the cohort retrospectively (LOE III) [21–23,27–29], and 2 were case series (LOE IV) [10,25]. Five studies out of 10 compared clinical outcome of UKA and TKA cohorts [22–24,28,29]. Six studies reported specific RTS outcome like preoperative and postoperative sport participation, RTS rate, time to RTS and pre and postoperative sport-specific participation [10,21,22,27–29]. Canetti et al. compared two different cohort of lateral UKA performed with and without robotic assistance [21].

3.3. Demographic Results

Overall number of patients analyzed in the present review was 5220 with 2930 UKA and 2447 TKA implanted. Mean age of UKA's was 66.3, whereas mean age of TKA cohort was 74 years old. Mean follow-up was 2.1 years. In three studies type of prosthesis was not specified [22,24,29] while 4 papers reported outcome of mobile bearing UKA [25–28]. Demographic parameters of included study are summarized in Table 1.

Table 1. Demographic studies details.

Author and Year	LOE	Ner of Patients	M	F	Type of Arthroplasty	Type of Implant	Bearing and Fixation	Mean Age at Surgery	Mean Follow-up (Months)	MINORS Score
Canetti et al. 2018	3	25 (28 knees)	9	21	Robotic UKA 11 Conventional UKA 17 UKA 420	Resurfacing Uni Evolution, Tornier; BlueBelt Navio robotic surgical system.	Fixed bearing and cemented.	66.5 ± 6.8 59.5 ± 9.9 67 ± 10	34.4 ± 10.5 39.3 ± 15.5	17
Harbourne et al. 2018	3	995	6	9	TKA 575	n/a	n/a	70 ± 9	12	16
Lygre et al. 2010	3	1344	152	220 690	UKA: 372	Genesis Uni (Smith & Nephew), Miller-Galante all poly Uni (Zimmer), Oxford III (Biomet).	Fixed/mobile and cemented.	68.8 ± 8.8	58.8 ± 27.6	15
Matthews et al. 2013	2	68	282	10	TKA: 972	AGC (Biomet), Genesis I (Smith & Nephew), LCS (DePuy) and NexGen (Zimmer).	Fixed bearing and cemented.	76 ± 7.7	84 ± 28.8	15
Naal et al. 2007	4	83 (83)	14	20	TKA 34	n/a	n/a	UKA 67.3 ± 9.1 TKA 69.2 ± 7.7	12	10
Pandit et al. 2011	4	818 (1000)	-	-	UKA	Preservation prosthesis (DePuy). Phase 3 Oxford medial UKA (Biomet)	Fixed bearing and cemented. Mobile bearing and cemented.	65.5 ± 9.1 years (47–83) 66 (32–88)	12 67.2	11
Pandit et al. 2015	4	579 (520)	299	221	UKA	Phase 3 Oxford medial UKA (Biomet).	Mobile bearing and cementless	65.1 ± 10.3 (35–94)	40.8 ± 20.4	12
Pietschmann et al. 2012	3	131	57	74	UKA	Phase 3 Oxford medial UKA (Biomet).	Mobile bearing and cemented.	65.3 (44–90)	50.4 (12–120)	7
Walton et al. 2010	3	150 (183)	76	74	UKA	Phase 3 Oxford medial UKA (Biomet).	Mobile bearing and cemented.	71.5 ± 9.85	12	12
Wyde et al. 2008	3	120 (142) 48 966	61 59 511	59 52 355	TKA UKA: 100 TKA: 866	n/a n/a	n/a n/a	71.53 ± 9.87 66 (45–88) 69.6 (26–93)	24	16

UKA: Unicompartmental Knee Arthroplasty TKA: Total Knee Arthroplasty (TKA), LOE: Level of Evidence, M: Males, F: Females.

3.4. Return to Sport Activity

Sport-specific return rates were analyzed in 50% of the studies included [10,21,22,27–29]. Mean RTS rate for UKA was 89.5%, ranging from 75% [22,29] to 100% [28]. Mean preoperative sport participation rate was 71.8% of the patients, ranging from 36% [29] to 100% [21], and mean postoperative sport participation rate was 70.2% of the patients, ranging from 27% [29] to 100% [21]. Mean time to RTS was 6.2 months. Results of the study published by Canetti et al. [21], showed for UKA robotic assisted group a statistically significant difference in terms of time to return to sport compared to conventional UKA with a similar RTS rate (100% vs. 94%). The cohort of medial UKA of Pietschmann et al. [27] had an 88% of RTS rate with 80.1% of patients that returned to preoperative activity level. Naal et al. [10] reported RTS rate of 95%; moreover, the activity frequency (session per week) was maintained in postoperative assessment (2.9 vs. 2.8) with a slight decrease in terms of session length (66 vs. 55 minutes). Overall, by meta-analyzing available studies, we evidenced a good proportional RTS (0.86 95% CI 0.78, 0.94), with sport-specific RTS favoring those sports with low-impact. Meta-analysis results were showed in Figures 2–8.

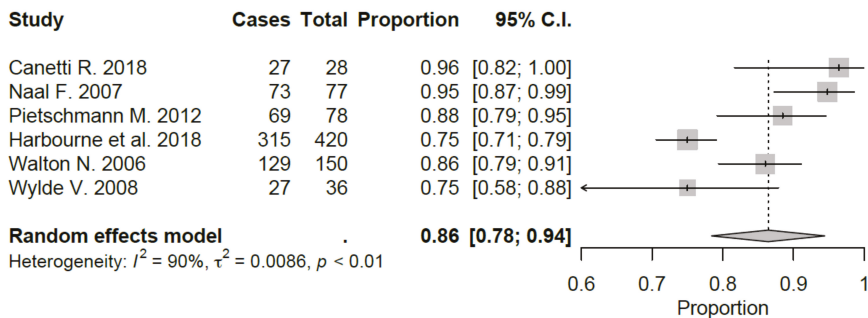


Figure 2. Overall return to sport after UKA (C.I.: Confidence Intervals).

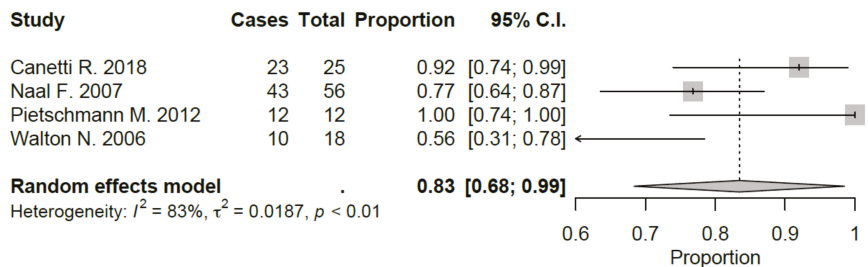


Figure 3. Return to hiking after UKA (C.I.: Confidence Intervals).

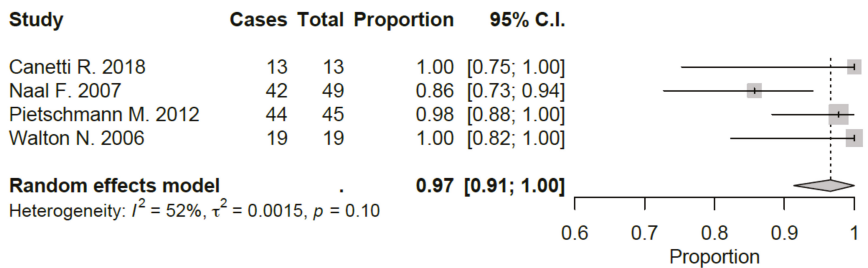


Figure 4. Return to cycling after UKA (C.I.: Confidence Intervals).

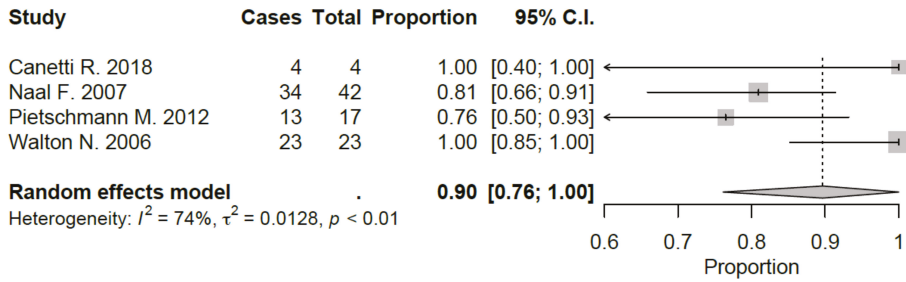


Figure 5. Return to swimming after UKA (C.I.: Confidence Intervals).

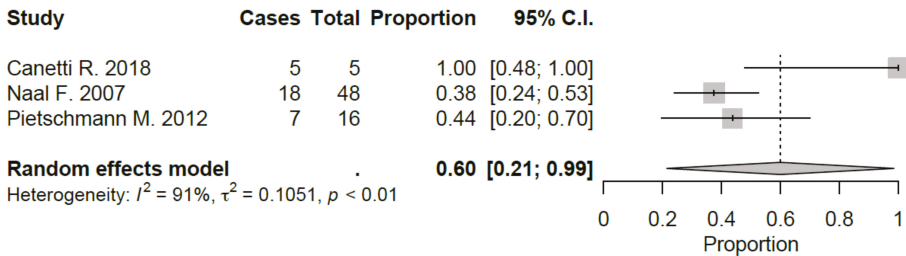


Figure 6. Return to alpine ski after UKA (C.I.: Confidence Intervals).

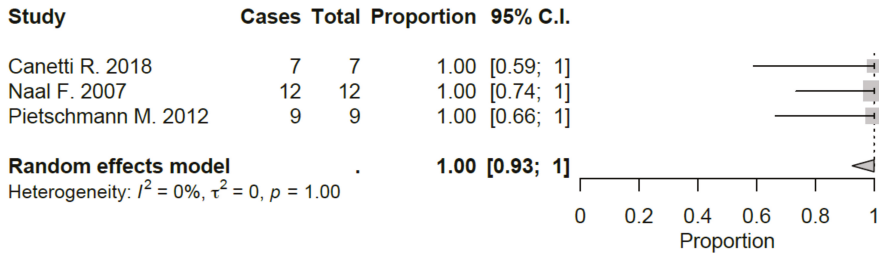


Figure 7. Return to fitness after UKA (C.I.: Confidence Intervals).

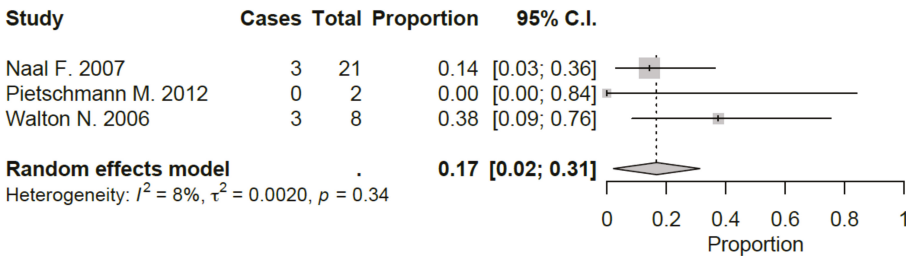


Figure 8. Return to tennis after UKA (C.I.: Confidence Intervals).

3.5. Comparison with TKA

Three papers compared RTS outcome of UKA and TKA patients' cohort [22,28,29]. Harbourne et al. [22] at 12 months of follow-up recorded a higher rate of return to activity in patients with UKA than TKA (75% vs. 59% $p < 0.001$). According to results of Walton et al. [28], the UKA group had a better percentage of patients that increased or maintained sport activity compared to the TKA group ($P_{.0003}$); moreover, TKA patients significantly reduced postoperative sport activity

compared to UKA's ($P_{.0001}$). Wylde et al. [29] investigated return to sport after different type of implant (THA, Hip Resurfacing, TKA, UKA) and no significant difference differences were detected in postoperative sport participation between UKA and TKA (75% vs. 73.1%). Meta-analysis study pooling showed a better RTS in patients undergoing UKA (Odds Ratio 2.14 95% CI 1.29, 3.55). Results are shown in Figure 9.

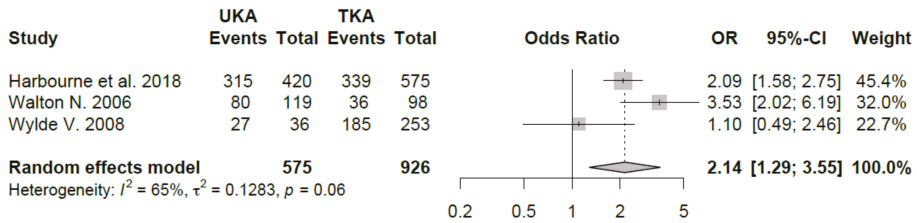


Figure 9. Return to sport after UKA vs. TKA (C.I.: Confidence Intervals, O.R.: Odds Ratio).

3.6. Clinical Outcome Data

Several clinical outcome assessment measure and sport specific questionnaires were utilized. Oxford Knee score were used in six studies [22,24–28], Knee Society Score (KSS) in five studies [10,21,24–27], WOMAC in three studies [21,24,27,29], Forgotten Joint Score (FJS) and UCLA in two studies [21,24], Tegner Activity Score in two studies [25,26], KOOS [23] and Lysholm Knee Scale [21] in one study. Clinical results of Canetti et al. [21] showed a higher IKSS-Objective (97.2 ± 5.9 vs. 91.2 ± 6.5 ; $p < 0.05$) and a higher IKSS-Objective improvement ($+ 30.9 \pm 7.7$ vs. $+ 22.8 \pm 12.2$; $p < 0.05$) compared to conventional group of lateral UKA. Naal et al. [10] obtained an improvement on KSS score in their postoperative assessment (from 129.9 ± 24.8 , vs. to 186.9 ± 18.3) with a good result in terms of quality of life stated with SF-36. Pandit et al. [26] obtained a good postoperative results with the first 1000 cases of Oxford phase 3 medial UKA at 5 years: mean OKS was 41.3 (SD 7.2), mean AKS Objective Score 86.4 (SD 13.4), mean AKS Functional Score 86.1 (SD 16.6), and mean Tegner activity score 2.8 (SD 1.1). The same group, in 2015 [25], published results of cementless fixation for the same implant with similar postoperative clinical and functional results: OKS 43 (SD 7), AKSS (objective) 81 (SD 13), AKSS (functional) 86 (SD 17), and Tegner activity score of 3 (1–8). Pietschmann et al. [27] had a higher postoperative OKS, KSS, WOMAC and UCLA score. Active patients in sport preoperatively, except for KSS knee objective score, obtained statistically significant higher score than inactive patients group (OKS < 0.01 , UCLA < 0.0001 , KSS function < 0.01 , KSS knee subjective < 0.01 , KSS overall < 0.01 , WOMAC < 0.05 , WOMAC stiffness < 0.05 , WOMAC ADL < 0.01 , WOMAC overall < 0.01). Results are summarized in Table 2.

3.7. Clinical Outcome Data UKA vs. TKA

Four studies compared clinical outcome in patients aged more than 65 years old and underwent to UKA and TKA [23,24,28,29]. In the patients' cohort of Lygre et al. [23], UKA had a statistically significant superiority over TKA in terms of KOOS "Symptoms" (adjust mean diff 2.7 $p = 0.04$), KOOS "Function in Daily Living" (ADL) (adjust mean diff 4.1 $p = 0.01$) and KOOS "Function in Sport and Recreation" (adjust mean diff 5.4 $p = 0.006$). A prospective study designed by Matthews et al. [24] showed no statistical difference according to satisfaction (89 vs. 87 $p = 0.41$) and perception of knee normality (69 vs. 68 $p = 0.99$) scores between UKA and TKA; nevertheless, UKA reached a statistically significant higher WOMAC ($p = 0.003$), SF-36 (physical $p < 0.001$; mental $p = 0.25$), Oxford knee ($p < 0.001$), American Knee Society (clinical $p = 0.002$; function $p < 0.001$) and Total Knee Function Questionnaire scores (ADL $p = 0.002$; sport and exercise $p = 0.02$; movement and lifestyle $p = 0.02$). Walton et al. [28] compared in their study Mini-Incision Unicompartmental Knee Arthroplasty versus TKA and reported better results in terms of OKS ($p = 0.0426$) and mean modified Grimby score

(3.89 SD:1.27 vs. 2.76 (SD:1.12). In the last comparative study, performed by Wylde et al. [29], no clinical difference between UKA and TKA in terms of WOMAC pain (81.5 SD = 20.8 vs. 81.6 SD = 19.3) and function (76.3 SD = 21.4 vs. 79.1 SD = 20.5).

Table 2. Functional outcomes of included studies.

Author and Year	N.er of Patients	Preoperative		Postoperative		Outcome
		Mean	SD	Mean	SD	
Canetti R. 2018	28	66.3	8.9	97.2	5.9	KSS-Objective
		84.6	11.3	96.4	9.2	KSS-Functional
		6.4	1.6	6.6	1.4	UCLA
Naal F. 2007	83	n/a	n/a	96.4	8.3	Lysholm scale
		129.9	24.8	186.9	18.3	KSS total
		24.7	8.7	38.6	8.4	OKS
Pandit H. 2011	1000	2.3	1.1	2	8.4	Tegner activity score
		68.7	18	81.1	11.3	AKSS-F
		47.4	20	81.1	16	AKSS-O
Pandit H. 2015	520	27	9	43	7	OKS
		3	n/a	3	n/a	Tegner activity score
		71	17	86	16	AKSS-F
Pietschmann M. 2012	131	52	20	92	12	AKSS-O
		n/a	n/a	95.3	9.5	KSS-Objective
		n/a	n/a	86.7	13.8	KSS-Functional
		n/a	n/a	6	1	UCLA
		n/a	n/a	189	26.8	KSS total
		n/a	n/a	38.6	7.3	OKS
n/a	n/a	90.6	9.7	WOMAC ADL		

S.D.: Standard Deviation, N/A: Not Available, OKS: Oxford Knee Score, KOOS: Knee injury and Osteoarthritis Outcome Score, KSS: Knee Society Score, AKSS: American Knee Society Score, UCLA: University of California Los Angeles, WOMAC: Western Ontario McMaster universities osteoarthritis index.

3.8. Quality Assessment (MINORS)

The MINORS score ranged from 7 [27] to 12 [25] for non-comparative studies and from 12 [28] to 17 [21] for the comparative ones (Table 1). The mean value was 10 for non-comparative studies and 15 for comparative studies. The funnel plot of studies evaluating RTS after UKA showed a symmetrical distribution, while a rather poor precision of observations, suggesting an overall low-moderate risk of methodological bias (Figure 10).

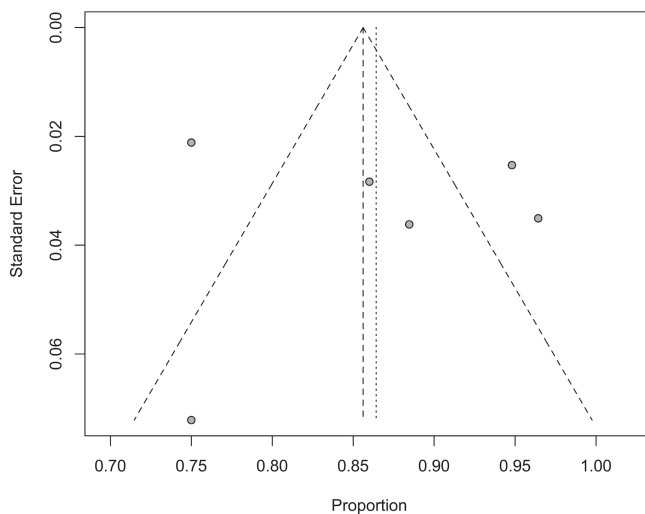


Figure 10. Funnel plot showing studies evaluating RTS after UKA.

4. Discussion

Elderly patients represent a selected population, which is changing in activity needs in recent years, according to general lifestyle modifications of the society. The main findings of the present investigation suggest a good proportional same level RTS in elderly patients after UKA (return proportion 0.86, 95%CI 0.78, 0.94), showing also better relative RTS and time to RTS of patients undergoing UKA, in comparison to those undergoing TKA. Moreover, patients undergoing TKA were more likely to reduce their activity level after the surgery [28]. Meta-analysis of the sport-specific RTS showed that higher return rates were observed for low-impact sports (e.g., swimming, fitness, hiking), whereas high-impact sports (e.g., tennis and alpine ski) prevented a full return to activities. The proportion of RTS for cohorts of patients undergoing UKA is in line with authors' experience and with literature-reported rates [10,21,30]. However, given the high heterogeneity of the studies concerning this outcome (90%), the result should be carefully interpreted. A first consideration concerns the average age of the cohorts, which was higher in those study reporting a lower RTS proportion. Furthermore, the differences in type of UKA implants could determine the activity level, with possible implications in polyethylene wearing [31]. Another major concern in general study heterogeneity is the absence, in almost all the studies, of a description of rehabilitation protocols and of surgical incision. In an era of wide differences in rehabilitation (i.e., fast-track, aquatic rehabilitation), understanding the post-operative protocols may be the key to evaluate the postoperative outcomes [32]. Moreover, the knee extension apparatus, thus the surgical approach plays a major role in return to activity and its timing.

Clinical outcomes reported in the included studies were filtered to collect those relative to sport participation and activity level. Although heterogeneous, an overall evaluation of the scores showed that either objective and subjective assessment improved significantly after UKA, suggesting that patient perception of the beneficial effects of the surgery reflects a standardized clinical examination and ROM assessment. Similarly, comparison of clinical outcomes after UKA with those after TKR favored the patients undergoing UKA. However, given the absence of control groups in most of the included studies, the meta-analysis evaluation was not possible, given the impossibility to calculate the standardized mean difference.

Concerning comparison of RTS and clinical outcomes between cohorts undergoing UKA and TKA, a potential confounding factor is age, as average age of UKA cohorts was 66.3 years, while mean age of TKA cohorts was 74 years. A 10-year difference is relevant by the observation that younger patients are more likely to continue in sport participation. This is especially true, given the higher and higher percentage of elderly population involved in sport activities in recent years [33]. Focusing on elderly population underlined some differences with available evidence on general population (non-elderly) [34,35]. First of all, as reported in previous literature reviews [11], the return to high-impact sport in patients that underwent either TKA and UKA was high, and not excessively different from those of low-impact sports [36,37]. Common experience leads the orthopedic surgeon to suggest caution in sport participation after joint arthroplasty, for the risk of component migration, loosening, and periprosthetic fractures. However, no specific evidence advises about long term results of sport involvement after UKA [30].

The UKA, a joint preserving arthroplasty, has been designed for those patients with localized osteoarthritis and was found especially beneficial in active individuals. However, the follow-up length reported in available literature is too short to assess failure and revision rates. It is opinion of the authors that until clear data will be available, the general attitude for patients and surgeon in regard to RTS will go toward a careful approach.

Another concern, in regards of the available literature, is the lack of information about reasons of not to return to sport activities. None of the articles included in this review reported the clinical and functional reasons that prevented the patients to return to activity, except a few reported surgical complications (i.e., common peroneal paralysis [21]). The issue of motivational causes that prevent RTS is relevant and only some studies in the gerontology field address the question [6,14]. An interesting

point to improve future research would be to introduce motivational and depression scales next to functional patient reported outcome measures.

The overall LOE of included studies was low, as most of the evaluations were retrospective or were case series. This is reflected in the relatively high risk of bias which MINORS score showed. In particular, the worst item was the blinding of participants. However, given the type of therapeutic intervention considered, blinding was impossible.

The funnel plot evaluation was limited to those studies assessing the proportional RTS of patients after UKA. A balanced funnel was observed at visual inspection, but a relatively low precision was found for some studies, suggesting an overall low–moderate risk of methodological bias.

This is the first literature review and meta-analysis that selected age of the cohorts undergoing UKA, focusing the research questions on the elderly population. Meta-analysis had a two-fold aim: to investigate proportional RTS in UKA-only cohorts and to compare UKA and TKA patients. However, the study was not free from limitations. First of all, the limited number of studies reporting sport-specific outcomes after UKA and the low LOE prevented the authors to gather a sufficient evidence to finally answer to the research questions. Furthermore, the differences in study design, age of the cohorts and effect sizes yielded to high heterogeneity and prevented to draw a robust overall meta-analysis.

5. Conclusions

UKA is a valid and reliable option for elderly patients to satisfactorily resume their sport practice, especially for low impact activities. The rate of return to sports following UKA is higher than TKA. The most practiced sports after surgery are low contact activities such as swimming, fitness, and hiking. Unfortunately, there is a lack of consistent clinical data on the functional improvement before and after surgery in elderly patients, thus a standardized evaluation of patient after surgery is prevented. More, prospective, comparative studies are needed to determine the standardized functional improvement of elderly patients after UKA.

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Review

The Effects of Physical Exercise on Balance and Prevention of Falls in Older People: A Systematic Review and Meta-Analysis

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Abstract: The aims of this systematic review and meta-analysis were to evaluate the effects of physical exercise on static and dynamic balance in the elderly population, and to analyze the number of falls and fallers. A systematic literature search was conducted using PubMed–Medline, Cochrane Central, and Google Scholar to select randomized clinical trials that analyzed the role of exercise on balance and fall rate in patients aged 65 or older. Sixteen articles were included in this review. Applying the Cochrane risk-of-bias tool, three studies were determined to be at low risk of bias, nine at unclear risk of bias, and four at high risk of bias. The meta-analysis showed improvements in dynamic balance ($p = 0.008$), static balance ($p = 0.01$), participants' fear of falling ($p = 0.10$), balance confidence ($p = 0.04$), quality of life ($p = 0.08$), and physical performance ($p = 0.30$) in patients who underwent physical exercise compared to controls. The analysis of the total numbers of falls showed a decreased likelihood of falls in patients who participated in exercise programs ($p = 0.0008$). Finally, the number of patients who fell at least once was significantly reduced in the intervention group ($p = 0.02$). Physical exercise is an effective treatment to improve balance and reduce fall rates in the elderly.

Keywords: physical exercise; balance; falls; older people; systematic review; meta-analysis

1. Introduction

Increasingly, attention is being paid by the scientific community to aging, and especially to successful aging. Several interventions aimed to improve the physical and psychosocial status of the elderly have been developed [1]. The decline in physical performance and cognitive capabilities with age causes progressive impairment of muscle strength, coordination, and balance [2], exposing people to a higher risk of falls [3,4]. Human balance is a complex multidimensional concept related to postural control, and it refers essentially to the ability to maintain a posture (e.g., sitting or standing), move between postures, and not fall when reacting to an external disturbance [5]. Apart from the risk of fractures [6] associated with falls, balance represents one of the main features of a plethora of daily activities, both professional and recreational; thus, an impairment of this ability could have a detrimental effect on quality of life [7]. A clear definition has been proposed for a "fall", namely "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects" [8]. Almost one out of three elderly people experience a fall

every year [9,10], while a person who experiences at least two falls within 6 months is defined as a “recurrent faller” [11,12]. Falls in older people are concerning events that could result in fractures, residual disability, chronic pain, and loss of independence, leading to important social and public health consequences requiring expensive long-term treatments [13] and accounting for 40% of all injury-related deaths in this group. The severity of the injuries derived from falls vary considerably from minor cutaneous injuries to major fractures, and, in some cases, to fatal traumas [14]. For those patients affected by osteoporosis, the risk of femoral fractures or vertebral body fractures is high, especially for ground-level falls or falls on stairs. The risk for head trauma is consistent across the whole elderly population, and such injuries may result in intracranial pathology with functional sequelae [15]. Progressive physical impairment can happen because of inactivity, which is recognized to be a factor in decreased body function in the elderly [16,17]. Indeed, physical exercise (PE) plays a fundamental role in the prevention of several age-related pathologies, such as metabolic and cardiovascular disease, cancer, and loss of bone quality, to such an extent that the proclamation “exercise is medicine” has been made [18,19]. There is overwhelming evidence that physical exercise can lower the risk of falling in elderly people, averting muscle mass reduction, and improving balance control. In particular, leg strength training seems to be crucial in preventing falls, as lower-limb weakness has been identified as a significant risk factor for falling [20]. In particular, the risk of falling can be assessed using postural control markers. For instance, it has been demonstrated that the risk of a fall is more than doubled when the timed up-and-go (TUG) test requires ≥ 13.5 s to be completed, the gait speed is < 1 m/s, and the modified Romberg test shows a standing time of ≤ 19 s [21,22]. Furthermore, balance training (BT) has been investigated in recent years [23,24] as an important intervention to slow the physiological decline of balance control in the elderly, and has been revealed to be an effective option for improving balance and postural control [25,26]. Aging involves some changes that affect balance; these include rigidity and reduced range of articular motion, sarcopenia and impaired muscle strength [27,28] cognitive decline, and changes in sensory systems, such as poor vision and hearing [29]. Thus, many systematic reviews and meta-analyses have reported that BT plays a crucial role and it is recommended among other interventions to reduce the risk and rate of falls in older adults [24,30]. We present an updated systematic review and meta-analysis with the aim to analyze the effect of physical exercise on static and dynamic balance in patients aged 65 years or over. The primary endpoint was the improvement of balance performance after various types of physical exercise. The secondary endpoint was the number of falls and/or fallers before and after a course of physical exercise.

2. Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [31] and was performed using the PRISMA checklist (Table S1). In this manuscript, we included randomized clinical trials (RCTs) that evaluated the effect of physical exercise on static and dynamic balance and on the number of falls and fallers in the elderly.

2.1. Inclusion Criteria

The inclusion criteria were RCTs in the English language published in the past decade, which analyzed the effects of land-based or aquatic exercise on balance and falls rate on patients aged 65 or older, according to the World Health Organization (WHO) definition of the elderly. Exclusion criteria were studies that involved patients with Parkinson’s or Alzheimer’s disease, dementia, hemiplegia, cancer, fibromyalgia, or following a stroke, spinal cord injuries, or fractures. We excluded studies that evaluated activities such as tai chi, yoga, pilates, or dance.

2.2. Search Methods

A systematic literature search was conducted using the following online databases: PubMed–Medline, Cochrane Central, and Google Scholar. We used the following search strings:

("Balance" (Journal) OR "balance"(All Fields)) AND ("exercise"(MeSH Terms) OR "exercise"(All Fields) OR ("physical"(All Fields) AND "activity"(All Fields)) OR "physical activity"(All Fields)) AND ("aged"(MeSH Terms) OR "aged"(All Fields) OR "elderly"(All Fields)). Moreover, the following filters were used: randomized controlled trial (article types); 2010/01/01 to 2020/05/01 (publication dates); aged: 65+ years (ages); English (languages); humans (species). The reference lists of the included RCTs were checked in order to select further studies for inclusion. After duplicates were removed, two reviewers (G.P. and S.V.) independently read the abstracts of studies appropriate for inclusion. Differences of opinion were resolved by discussion with the third review author (R.P.). Finally, the full articles were checked by two investigators (G.P. and S.V.) in order to choose the studies to be included in the review and meta-analysis.

2.3. Data Collection, Analysis, and Outcomes

Two review authors (G.P. and S.V.) independently performed data extraction. The following data were extracted from the included studies: authors, year of publication, type of study, level of evidence, numbers of participants and their age and sex in both study and control groups, previous falls, follow-up, and intervention(s) in the experimental and in the control group. Many outcomes were analyzed for the assessment of static and dynamic balance, participants' fear of falling, physical performance, quality of life, and risk of falls. Finally, total number of falls, number of fallers, and fall rate (falls per person-year) were compared between exercise and control groups.

2.4. Risk of Bias Assessment

The risk of bias of the included RCTs was independently assessed by two investigators (G.P. and S.V.) by the Cochrane risk-of-bias tool [32]. This tool consists of seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding for outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each item was graded as having a low, unclear, or high risk of bias. Thus, the trials presented low risk of bias if six or seven domains were reported to have low risk of bias, unclear risk of bias if four of five domains were at low risk of bias, or high risk of bias if fewer than four domains were at low risk of bias.

2.5. Statistical Analysis

A meta-analysis was conducted using the Review Manager (RevMan) software Version 5.3. Continuous outcomes were used to assess effects on static and dynamic balance, fear of falling, physical performance, quality of life, and risk of falls between the experimental and the control groups. Dichotomous outcomes were used to assess the total number of falls and the number of fallers between the two groups. Due to the use of different scores for the various outcomes, the continuous data are shown as standard mean difference (SMD) with 95% confidence intervals. Negative values of SMD indicate a benefit for the intervention group. Dichotomous data are presented as odds ratio (OR) with 95% confidence intervals. For the calculation of the weight of the samples of the trials, falls or fallers per month of follow-up were used instead of the total events. The I^2 test was used to evaluate heterogeneity. In the presence of low heterogeneity ($I^2 < 55\%$), we used a fixed-effect model; otherwise, a random-effect model was applied. The statistical significance of the results was set at $p < 0.05$.

2.6. Quality Assessment

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) assessment was used to evaluate the quality of the evidence of the outcomes and strength of recommendation [33]. This tool evaluates five items for each outcome: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each component was classified as not serious, serious, or very serious. The GRADE allocates the quality of evidence for the outcomes as high, moderate, low, or very low. RCTs were assigned an initial ranking of high, which could be downgraded for the items mentioned above.

3. Results

3.1. Results of the Search

The literature search yielded 1397 articles. After the removal of duplicates, the titles and abstracts of 1267 of these were examined, leading to the selection of 69 eligible papers that were read in full. Subsequently, 53 studies were excluded for the following reasons: not reporting selected outcomes ($n = 17$), not evaluating land-based or aquatic exercise ($n = 11$), patients aged below 65 years ($n = 9$), protocols of RCT ($n = 7$), and case reports ($n = 2$). Finally, 16 articles were included in this review and meta-analysis (Figure 1).

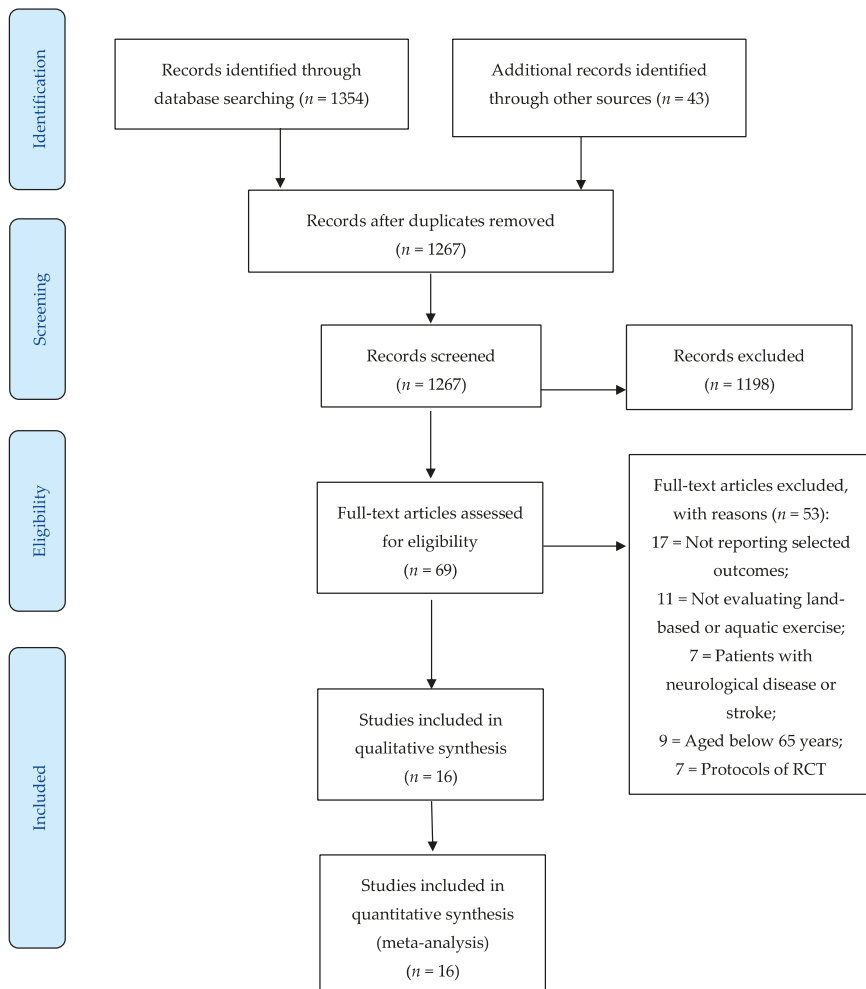


Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram.

3.2. Demographic Data

The total number of participants in all the included studies was 2960, of which 1521 were in the combined exercise group and 1439 in the combined control group. The ages of the patients ranged from 67.3 to 86 years in the intervention groups, and from 67.2 to 86 in the control groups. The percentages

of women in the trials ranged from 50% to 100% in the experimental groups and from 44% to 100% in the control groups. These data indicate a higher inclusion of females for the evaluation of the reported outcomes, and there were four studies that included only elderly women. The percentage of patients that had fallen at least once in the previous year was heterogeneous between the studies, ranging from 13.6% to 62% in the exercise groups and from 12.4% to 69% in the control groups. The demographic characteristics of the patients at baseline are reported in Table 1.

3.3. Physical Activity Program

Fourteen studies evaluated land-based exercise, while the remaining two studies [34,35] examined aquatic exercise (Table 2). Regarding exercise protocols, the patients in three trials participated in the Otago Exercise Program (OEP) [36–38], while in the other studies, the patients participated in different types of strength and balance training exercise programs. The mean follow-up was 9.2 months and ranged from 4 weeks to 2 years.

3.4. Clinical Outcome Data

The mean outcome measures before and after treatment are reported in Table 3. Dynamic balance was assessed in nine studies, using timed up-and-go (TUG) test [35,37–41], TUG-motor [42], TUGcog [34], or 8 foot up-and-go test [43]. Static balance was evaluated via Berg balance score (BBS) in six studies [34,37,40,41,43,44]. Participants' fear of falling was assessed in five studies, using the Falls Efficacy Scale—International (FES-I) [39,45], Modified Falls Efficacy Scale (MFES) [46], Falls Efficacy Scale, Swedish version (FES(S)) [36], and Thai Falls Efficacy Scale (Thai FES-I) [37]. Balance confidence was reported in four studies, using the Activities-Specific Balance Confidence (ABC) Scale [34,35,46] and short-ABC [47]. Quality of life was assessed in three studies using the Short-Form-36 (SF-36) [39,45] or Short-Form-12 (SF-12) [40] Health Survey. Physical performance was evaluated in three studies, using the Short Physical Performance Battery (SPPB) [36,38,45].

3.5. Methodological Evaluation

Upon applying the Cochrane risk-of-bias tool, three studies (18.75%) were determined to be at low risk of bias (A), nine studies (56.25%) were at unclear risk of bias (B), and four studies (25%) were at a high risk of bias (C) (Table 4). More specifically, random sequence generation was adequate in all the studies except one (93.75%). Allocation concealment was considered adequate in 14 trials (87.5%). Blinding for participants and personnel appeared to be impossible due to the nature of the intervention; thus, it was inadequate in 15 studies (93.75%). Blinding for outcome assessment was graded as adequate in 13 studies (81.25%). Incomplete outcome data were judged as adequate in eight studies (50%). Selective reporting was considered adequate in 11 studies (68.75%). Other sources of bias were adequate in eight trials (50%).

Table 1. Demographic characteristics of the patients at baseline.

Author (Year)	Type of Study	LOE	Study Group			Control Group			Fell at least Once in Past Year	
			n	Age	Sex	n	Age	Sex	Study	Control
Ansai et al., (2015) [42]	RCT	I	23	81.9 y	73.9% F, 26.1% M	23	82.6 y	65.2% F	10 (43.5%)*	8 (34.8%)
			23	82.8 y	65.2% F, 34.8% M			34.8% F	7 (30.4%)*	*
Arkkukangas et al., (2019) [36]	RCT	I	61	83 y	67% F, 33% M	56	82 y	73% F, 27% M	24 (39%)	21 (37%)
Arnold et al., (2010) [34]	RCT	I	28	73.2 y	71.4% F, 28.6% M	25	75.8 y	64% F	14 (50%)*	9 (36%)
			26	74.4 y	77% F, 23% M			36% M	16 (62%)	
Boongird et al., (2017), [37]	RCT	I	219	74.08 y	83.6% F, 16.4% M	220	73.94 y	81.4% F, 18.6% M		
Clemson et al., (2010) [46]	RCT	I	18	81 y	50% F, 50% M	16	82 y	44% F, 56% M	7 (39%) +	4 (25%) +
El-Khoury et al., (2015) [39]	RCT	I	352	79.8 y	100% F	354	79.6 y	100% F	137 (39%)	159 (45%)
Gianoudis et al., (2014) [48]	RCT	I	81	67.7 y	64% F, 36% M	81	67.2 y	73% F, 27% M	11 (13.6%)	10 (12.4%)
Hale et al., (2012) [35]	RCT	I	23	73.6 y	74% F, 26% M	16	75.7 y	75% F, 25% M	13 (61%)	11 (69%)
Hewitt et al., (2018) [45]	RCT	I	113	86 y	62.8% F, 37.2% M	108	86 y	68.2% F, 31.8% M	69 (61%)	54 (50.5%)
Jacobson et al., (2011) [43]	RCT	I	14	83.05 y	57.1% F, 42.9% M	11	81.37 y	72.7% F, 27.3% M		
Leiros-Rodriguez et al., (2014) [40]	RCT	I	14	69 y	100% F	14	68 y	100% F		
Liu-Ambrose et al., (2019) [38]	RCT	I	172	81.2 y	64% F, 36% M	172	81.9 y	69% F, 31% M	43 (25%)	60 (35%)
Miko et al., (2018) [41]	RCT	I	50	69.33 y	100% F	50	69.10 y	100% F		
Patil et al., (2015) [49]	RCT	I	205	74.4 y	100% F	204	74 y	100% F		
Patti et al., (2017) [44]	RCT	I	49	67.32 y	53% F, 47% M	43	68.93 y	55.8% F, 44.2% M		
Smulders et al., (2010) [47]	RCT	I	50	70.5 y	90% F, 10% M	46	71.6 y	97.8% F, 2.2% M		

RCT: randomized clinical trial; LOE: levels of evidence; N.: number of participants; y: years; F: female; M: male. * = fall in the past 3 months; + = frequent falls (≥3) in the past 12 months.

Table 2. Clinical results of the included studies.

Author	Intervention(s)	Control	Follow-up	Results
Ansai	Multicomponent training: protocol consisting of warm-up, aerobic, strength, balance, and cool-down exercises for 16 weeks Resistance training: leg press, chest press, calf, back extension, abdominal, and rowing for 16 weeks	No intervention	22 w	There were no significant differences between groups and assessments in any variable.
Arkkukangas	OEP: home-based exercise program designed to improve strength, balance, and endurance over 12 weeks	No intervention	12 w	In the short-term perspective, there were no benefits of an exercise program regarding physical performance, fall self-efficacy, activity level, hand-grip strength, and fall frequency in comparison to a CG.
Arnold	AE protocol consisted of lower- and upper-extremity strengthening, trunk-control, and balance exercises twice a week for 11 weeks (preceded by educational session in the aquatics and education group)	No intervention	11 w	Significant improvement in fall risk factors ($p = 0.038$) with the combination of aquatic exercise and education.
Boongird	Modified OEP: five combined leg-muscle strengthening, balance retraining, and stretching exercises, which progressed in difficulty, and a walking plan	Fall prevention education	12 m	The incidence of falls was 0.30 falls per person year in the EG, compared with 0.40 in the CG. The fear of falling was significantly lower in the EG than CG ($p = 0.003$).
Clemson	Lifestyle Approach to Reducing Falls through Exercise (LiFE) program: home-based balance and strengthening exercise program for fall prevention	No intervention	6 m	The relative risk analysis demonstrated a significant reduction in falls in EG (RR = 0.23). Dynamic balance improved for the LiFE program participants ($p = 0.04$).
El-Khoury	Ossebo program: weekly supervised group sessions of progressive balance training for two years, supplemented by individually prescribed home exercises	No intervention	24 m	The injurious fall rate was 19% lower in the EG than in the CG ($p = 0.04$). The EG fared significantly better than the CG in all balance and gait performance tests.
Gianoudis	Multimodal program incorporating high-velocity progressive resistance training, weight-bearing impact and/or balance training, and fall-prevention exercises, performed three days per week for 12 months	Standard care self-management	12 m	There were no significant differences in fall incidence between the groups, or in the number of participants sustaining one or more falls or multiple falls.
Hale	Water-based exercise classes twice weekly for 12 weeks	Time-matched computer training program for 12 weeks	12 w	Water-based exercise did not reduce falls risk compared with attending a computer-skills training class.
Hewitt	Resistance training plus balance exercises performed in a group setting for 50 h over a 25-week period (Sunbeam program), followed by a maintenance period for 6 months	Regular activity schedule	12 m	Overall incidence of falls in the EG of 1.31 per person-year, compared with 2.91 in the CG. A significantly greater improvement was found in physical performance in the EG than in the CG ($p = 0.02$).

Table 2. Cont.

Author	Intervention(s)	Control	Follow-up	Results
Jacobson	Standing, static balancing, and mild leg exercise, 12 min per session, three times per week for 12 weeks.	Regular group exercise	12 w	Significant ($p < 0.01$) improvement for the EG over the CG in the 30 s chair test repetitions, 8-foot up and go test, balance assessment, and leg-function assessments.
Leiros-Rodriguez	12 sessions of balance exercises for 50 min	No intervention	4 w	Berg Balance Scale, timed up-and-go test, and SF-12 showed statistically significant differences in the EG ($p < 0.05$).
Liu-Ambrose	Usual care plus OEP (a home-based strength and balance retraining exercise program) for 12 months	Fall-prevention care	11 m	Fall rates were lower in the EG compared with CG (IRR, 0.64; $p = 0.009$). The estimated fall rate incidence was 1.4 per person-year in the EG and 2.1 in the CG ($p = 0.006$).
Miko	12-month of balance-training exercise program (three times a week for 30 min)	No intervention	12 m	TUG and BBS test scores showed a statistically significant difference between EG and CG ($p < 0.005$). The event rate for the number of patients who fell was 0.122 in the EG and 0.229 in the CG, thus the relative risk of falls was 0.534 ($p = 0.17$).
Patil	Group exercise classes twice a week for 12 months and once a week for the subsequent 12 months and home exercises	Current physical activity	24 m	Timed up-and-go and grip strength did not differ between groups. There was no difference in the total falls incidence rate ratio (IRR = 1.0).
Patti	Joint mobility, cardiovascular exercise, strengthening of core stability, proprioceptive training, and eye-hand/eye-foot coordinative exercises for 13 weeks	No intervention	14 w	Only the EG group demonstrated significant improvements in balance skills ($p < 0.00001$).
Smulders	11 sessions over 5.5 weeks of education, obstacle course, walking exercises, weight-bearing exercises, correction of gait abnormalities, and training in fall technique	No intervention	12 m	The fall rate in the exercise group was 39% lower than for the control group (0.72 vs 1.18 falls/person-year; risk ratio of 0.61).

OEP: Otago Exercise Program; AE: aquatic exercise; w: weeks; m: months; CG: control group; EG: experimental group.

Table 3. Outcome measures before and after treatment.

Study	TUG (s)	BBS (pts)	FES (pts)	ABC (pts)	SF-36/SF-12 (pts)	SPPB ⁹ (pts)
Ansai	I	30.4 ± 12.2	29.8 ± 13.1			
	C	29.0 ± 15.5	26.7 ± 22.2			
Arkkukangas	I	25.3 ± 8.4	25.3 ± 9.3	103.3 ± 21.3 ¹	106.5 ± 20.9	7.9 ± 2.4
	C			100.2 ± 26.5	106.2 ± 20.6	7.6 ± 2.5
Arnold	I	14.9 ± 5.6	12.6 ± 3.9	30.4 ± 3.8	31.4 ± 3.2	69.2 ± 19.9 ⁵
	C	15.8 ± 9.1	15.1 ± 9.5	29.3 ± 5.2	30.5 ± 5.1	70.4 ± 21.9
	I	14.3 ± 6.7	14.5 ± 7.1	31.1 ± 2.7	30.9 ± 3.8	65.3 ± 18.1
	C					62.9 ± 20.8
						75.0 ± 15.2
						69.6 ± 24.4
						8.1 ± 2.8
						8.2 ± 2.6

Table 3. Cont.

Study	TUG (s)		BBS (pts)		FES (pts)		ABC (pts)		SF-36/SF-12 (pts)		SPPB ⁹ (pts)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Boongird	I	16.75	16.7	21.68	27.11 ²	24.7						
	C	16.6	16.8	21.48	26.84	27						
Clemson	I				45.3 ± 8.2 ³	50.3 ± 5.18	925 ± 341 ⁶	1125 ± 233				
	C				45.1 ± 8.7	46.6 ± 4.81	825 ± 372	830 ± 149				
El-Khoury	I	12.38 ± 2.76	11.93 ± 3.23		25.52 ± 7.06 ⁴	26.58 ± 6.37			57.05 ± 15.80 ⁷	55.65 ± 14.87		
	C	12.39 ± 3.09	12.69 ± 3.22		26.02 ± 6.97	27.46 ± 6.33			54.72 ± 16.05	53.56 ± 14.71		
Hale	I	11.0 ± 3.13	10.1 ± 2.9				64.2 ± 19.3 ⁵	67.0 ± 19.95				
	C	10.7 ± 5.78	10.7 ± 6.84				66.4 ± 19.8	66.7 ± 13.23				
Hewitt	I				27.75 ± 10.08 ⁴	30.01 ± 9.67			65.72 ± 18.30 ⁷	74.66 ± 18.51	5.16 ± 2.57	5.81 ± 3.02
	C				31.28 ± 13.03	30.57 ± 9.69			64.96 ± 16.98	72.43 ± 16.60	4.30 ± 2.90	4.13 ± 2.92
Jacobson	I	16.97 ± 5.63	12.71 ± 3.07	26.91 ± 3.65	40.67 ± 6.10							
	C	16.20 ± 3.67	18.26 ± 5	27.24 ± 4.64	24.42 ± 7.78							
Leiros-Rodriguez	I	11 ± 1.3	6.71 ± 0.73	45.86 ± 2.91	54.07 ± 1.98				49.36 ± 3.2 ⁸	54.93 ± 1.8		
	C	11.14 ± 1.68	10.93 ± 1.49	47.79 ± 3.38	47.71 ± 2.89				50.29 ± 2.5	50.79 ± 2.3	7.9 ± 2.2	7.9 ± 2.2
Liu-Ambrose	I	16.3 ± 7	16.1 ± 6								7.8 ± 2.3	7.8 ± 2.4
	C	16.9 ± 6.4	16.6 ± 8.5									
Miko	I	8.89 ± 7.38	6.74 ± 3.13									
	C	9.95 ± 12.02	10.64 ± 13.84									
Patti	I			51.83 ± 4.17	54.36 ± 2.15							
	C			51.09 ± 3.89	51.67 ± 4.49							
Smulders	I						54.3 ± 19.7 ⁵	61.9 ± 16.9				
	C						55.5 ± 22.1	55.5 ± 22.8				

I: intervention group; C: control group; TUG: timed up-and-go; BBS: Berg Balance Score; FES: Falls Efficacy Scale; ABC: Activities-Specific Balance Confidence; SF-36/SF-12: Short Form-36/Short Form-12 Health Survey; SPPB: Short Physical Performance Battery; s: seconds; pts: points; FES: ¹ = FES Swedish version (0–130); ² = Thai Falls Efficacy Scale (16–64); ³ = Modified Falls Efficacy Scale (0–140); ⁴ = FES-1 (16–64); ABC: ⁵ = ABC (0–100); ⁶ = ABC (0–1600); SF-36: ⁷ = SF-36 (0–100); SF-12: ⁸ = SF-12 (0–100); SPPB: ⁹ = SPPB (0–12).

Table 4. Cochrane risk-of-bias tool for randomized controlled trials.

Study	Random Sequence Generation	Allocation Concealment	Blinding (Participants and Personnel)	Blinding (Outcome Assessment)	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias	Risk of Bias
Ansai	L	L	H	L	L	H	U	B
Arkkukangas	L	L	H	L	L	L	U	B
Arnold	L	L	H	L	L	U	L	B
Boongird	L	L	H	L	U	L	L	B
Clemson	L	L	H	L	H	L	U	B
El-Khoury	L	L	H	L	L	L	L	A
Gianoudis	L	U	H	U	U	L	L	C
Hale	L	L	H	L	U	L	L	B
Hewitt	L	L	H	L	L	L	L	A
Jacobson	L	L	H	H	L	H	L	B
Leiros-Rodríguez	L	U	H	U	L	L	U	C
Liu-Ambrose	U	L	H	L	L	L	L	A
Miko	L	L	H	L	H	L	U	B
Patil	L	L	U	L	H	U	U	C
Patti	L	L	H	L	H	U	U	C

L: low; U: unclear; H: high.

3.6. Effect of Intervention

The meta-analysis showed the effect of exercise on dynamic balance, static balance, participants' fear of falling, balance confidence, quality of life, and physical performance compared to controls (Figure 2). TUG times decreased significantly in the intervention group, demonstrating significant improvements in dynamic balance in comparison with the control group (SMD -0.51 , 95% CI -0.88 to -0.13 , $p = 0.008$). BBS showed significant improvements in static balance for the exercise group (SMD -1.29 , 95% CI -2.29 to -0.29 , $p = 0.01$). FES showed better fear-of-falling outcomes in patients who did physical exercise compared to controls (SMD -0.13 , 95% CI -0.28 to 0.03), but no significant differences ($p = 0.10$). Balance confidence, assessed by ABC, showed significant differences in favor of the experimental group (SMD -0.52 , 95% CI -1.01 to -0.03 , $p = 0.04$). Short-Form Health Survey results showed greater improvements in quality of life in the experimental groups (SMD -0.48 , 95% CI -1.01 to -0.05), without significant differences ($p = 0.08$). SPPB showed no significant differences in physical performance between the two groups ($p = 0.30$), but better outcomes in the exercise group (SMD -0.19 , 95% CI -0.56 to 0.17). Summarily, analyzing all the reported scores, a significant difference was shown in favor of the physical exercise group compared to the controls ($p > 0.00001$).

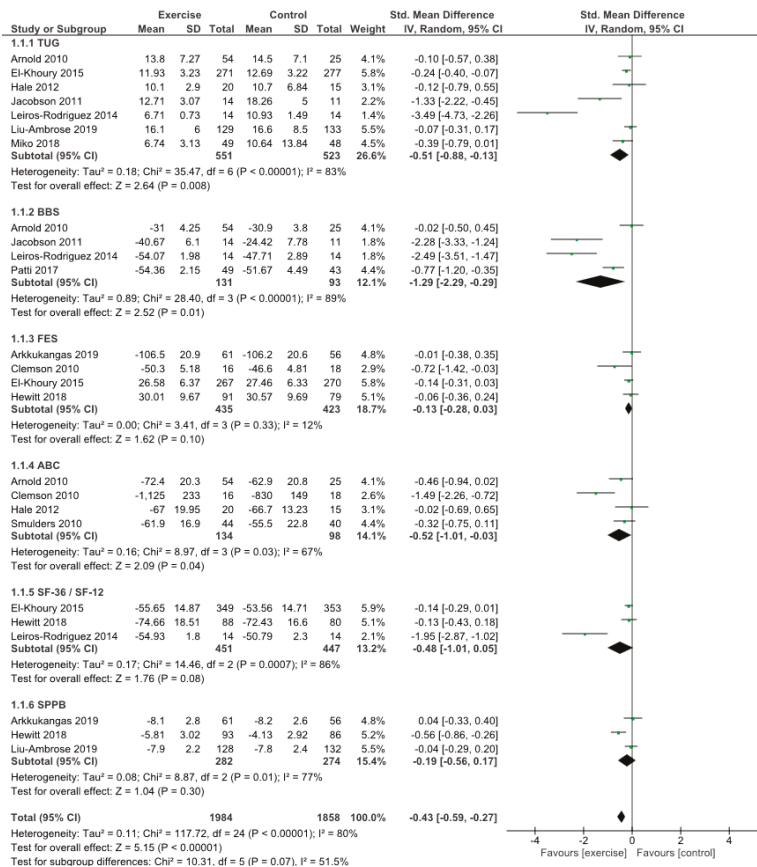


Figure 2. Outcome measurements.

The analysis of the total numbers of falls showed a statistically significant decreased likelihood of falls in patients who participated in exercise programs (OR 0.64, 95% CI 0.49 to 0.83, $p = 0.0008$) (Figure 3).

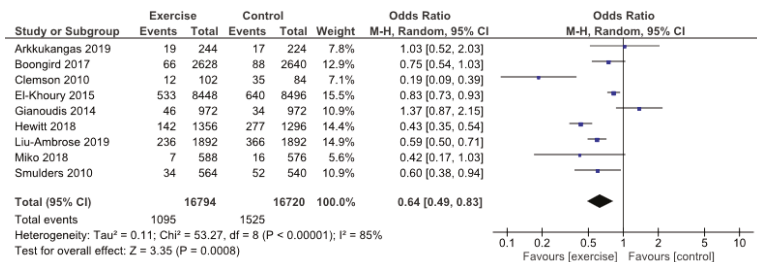


Figure 3. Total number of falls.

Finally, the number of patients who fell at least once was significantly reduced in the intervention group compared to the control group (OR 0.88, 95% CI 0.79 to 0.98, $p = 0.02$) (Figure 4).

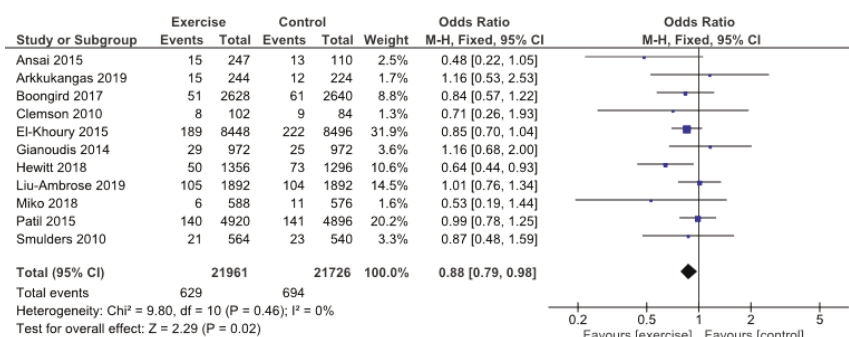


Figure 4. Number of fallers (≥1 falls).

3.7. Quality Assessment

The GRADE was used to assess the quality of the evidence provided in the included trials (Table 5). There were six comparisons for continuous data and two for dichotomous data. Regarding scores, TUG and BBS were downgraded by one level due to inconsistency of the results; thus, they reported a moderate quality. FES, ABC, and SPPB showed moderate quality because they were downgraded by one level for serious risk of bias. Finally, SF-36/SF-12 was downgraded by two levels due to serious risk of bias and inconsistency; thus, it presented low quality. In contrast, the outcomes of both total number of falls and fallers maintained a high quality of evidence.

Table 5. GRADE

Outcomes	Number of Participants (Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality
TUG	1074 (7 RCTs)	not serious	serious	not serious	not serious	not serious	⊕⊕⊕○ moderate
BBS	224 (4 RCTs)	not serious	serious	not serious	not serious	not serious	⊕⊕⊕○ moderate
FES	858 (4 RCTs)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕○ moderate
ABC	232 (4 RCTs)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕○ moderate
SF-36/SF-12	898 (3 RCTs)	serious	serious	not serious	not serious	not serious	⊕⊕○○ low
SPPB	556 (3 RCTs)	serious	not serious	not serious	not serious	not serious	⊕⊕⊕○ moderate
Total number of falls	2158 (9 RCTs)	not serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊕ high
Number of fallers (≥1 falls)	2632 (11 RCTs)	not serious	not serious	not serious	not serious	not serious	⊕⊕⊕⊕ high

TUG: timed up-and-go; BBS: Berg Balance Scale; FES: Falls Efficacy Scale; ABC: Activities-Specific Balance Confidence; SF-36/SF-12: Short Form-36/Short Form-12 Health Survey; SPPB: Short Physical Performance Battery; RCT: randomized clinical trial.

4. Discussion

The primary aim of this systematic review and meta-analysis was to evaluate the improvement of balance performance in the elderly population after various types of physical exercise. A secondary endpoint analyzed was the number of falls and/or fallers before and after an exercise program. Physical exercise was shown to be very beneficial for older people in terms of dynamic and static balance, fear of falling, balance confidence, quality of life, and physical performance, with a significant improvement reported for all the considered scores in patients who participated in a physical treatment compared to controls. The meta-analysis proved that the parameters for dynamic and static balance, such as TUG and BBS, demonstrated the best improvements after PE, with the most statistical significance compared to controls. In fact, balance training led to higher confidence in the participants' ability to perform various daily activities without falling, better patient mobility and safety at speed, greater ability to perform balance-related tasks, and lessened difficulties with activities of daily living. PE seemed to be particularly useful in reducing falls via the increase of postural control, more than improving quality of life and physical performance in older people. Moreover, with the exception of SF-36/SF-12 which was low, all the other outcomes presented a moderate quality of evidence as assessed by GRADE, thus supporting a recommendation of physical exercise in the geriatric population with risk of falls. The number of falls was recorded using daily fall calendars, which were returned to the blinded investigators. Regarding the evaluation of the number of falls and fallers, almost all the studies showed great improvements in the patients who underwent PE. Furthermore, the data showed both high quality and strength of recommendation according to GRADE for the benefit of balance and postural control exercises to reduce the rate of falls in the elderly. Only one study [48] reported no benefit in terms of falls and fallers after the exercise program, although it represented an effective approach for the improvement of multiple musculoskeletal and functional performance in older adults with risk factors for falls. Moreover, the meta-analysis showed that in patients who performed physical exercise, there was a statistically significant decrease in both the number of falls and fallers (respectively $p = 0.0008$ and $p = 0,02$). Furthermore, PE was more effective in reducing the total number of falls than the number of fallers, showing that improving muscle tropism and postural balance through specific protocol of exercises reduced the risk of falls, but it did not completely eradicate the risk of falling at least once. These data seem to strengthen the concept that PE represents a crucial aspect of prevention for reducing the risk of falls, which can lead to fractures and consequently to hospitalization, surgical procedures, and prolonged immobilization, with an increase in national healthcare costs. In contrast, a study by Lee et al. analyzed the effectiveness of exercise interventions on the rate of falls and number of fallers in care facilities, and they showed significant differences between all exercise interventions and control groups in the rate of falls, but they did not find differences in the number of fallers between all exercise interventions and control groups [50]. Similarly, Zhao et al. [51] showed that exercise had a positive effect on the reduction of fall-related fractures, with improvements in the rate of falls and leg strength in older people; however, they reported only a marginally beneficial effect of exercise on balance. Although the study population was represented by elderly people, the mean ages of the patients were different in the various studies. However, there was not a marked correlation found between age and greater improvements in the outcomes after balance training. Moreover, four studies enrolled only women, while the others included both sexes at various percentages. It seemed that in studies with only women, there were better improvements in the selected outcomes; therefore, the role of physical exercise and balance training could be greater in elderly women, and in the prevention of osteoporosis, reducing the risk of fracture following falls. In this systematic review, we included only RCTs in order to evaluate the role of physical activity compared to usual care. However, it was not possible to compare different kinds of physical activity in order to determine which is better for older people. In particular, only two studies analyzed aquatic therapy [34,35], which seems to be an interesting alternative to land-based exercise for the geriatric population, permitting low-impact and low-weight-bearing exercise. In fact, Guillaumon et al. [52] presented some evidence that aquatic exercise can improve modifiable risk factors of falls, although

the quality of this evidence was low, and there was a lack of consistency between studies. A limitation of this systematic review was the high variability of the training protocols of the included studies. Only few studies reported a fall-prevention program with a standardized protocol. The Otago Exercise Program was applied in three studies [36–38]; this is an individualized home-based program of balance and strength retraining exercises designed specifically to prevent falls [53]. Hewitt et al. [45] tested the Sunbeam program, which consists of individually prescribed progressive resistance training plus balance exercise. The Ossébo intervention, used by El-Khoury et al. [39], is composed of exercises designed to improve postural stability, muscle extensibility, balance, reaction time, coordination, and internal sense of spatial orientation [54]. The Lifestyle Approach to Reducing Falls through Exercise (LiFE) program, reported on by Clemson et al. [46], is a home-based, lifestyle-integrated balance and muscle-strengthening exercise training program specifically developed for fall prevention. Otherwise, the other studies did not refer to standardized exercise protocols, but they reported various generic exercises for postural balance, stationary strengthening [43], weight bearing [49], aerobic elements [41], and proprioceptive training and eye–hand/eye–foot coordinative [44]. Finally, Leiros-Rodríguez et al. [40] evaluated balance exercises as a recreational activity in public parks. Therefore, quite all the studies differed in terms of the applied exercise program; thus, it was difficult to compare the different results for the balance scores. Moreover, there was high heterogeneity among the studies in terms of the volume of training, due to different numbers of training weeks, sessions per week, exercises per session, repetitions per set, and sets per exercise, which resulted in varying loads of balance and strength training and fall-prevention exercises. Another limitation was the relatively short follow-up of some studies: it was one year or less in 87.5% of the studies, and may not allow the long-term effects of PA on dynamic and static balance to be determined. However, the overall quality of the included studies was good, with only four studies at a high risk of bias. The only critical item regarded the blinding for participants and personnel, which was at a high risk of bias in all the studies except one [49], but this was comprehensible for RCTs that compared clinical outcomes and the details of falls in patients who participated in specific exercise programs or no intervention. Instead, almost all studies used a clearly randomized allocation sequence and concealment, and the outcomes and falls were classified by qualified examiners (e.g., geriatricians or physical therapists) blinded to group assignment. Furthermore, the adherence to treatment in the studies was high and the patients lost to follow-up were few, demonstrating that PE protocols were well accepted by patients, despite their elderly age. In the literature search, we excluded many studies because they evaluated the role of PE only in patients with neurological or cardiovascular disease, whereas we were interested in analyzing the importance of exercise in the entire geriatric population, especially in healthy people, in order to limit the reduction of postural control and loss of muscle strength that predispose this population to an increased risk for falls [1]. We also focused on the differences between studies regarding the percentage of patients that had fallen at least once in the previous year. These data varied between 12.4% and 69% in the pretreatment measurements. Moreover, in many studies, this percentage was higher in the study group than in the control group; therefore, the result of fewer falls and fallers at follow-up in the study group acquires even more significance in light of these considerations. Valdés-Badilla et al. [55] reported the beneficial effects on quality of life, fall risk, activities of daily living, physical activity levels, and blood parameters of governmental physical activity programs for independent older adults. Finally, Tricco et al. [56] demonstrated that exercise was associated with a lower risk of injurious falls compared with usual care, but the type of physical activity used to reduce falls should be selected on the basis of patient and caregiver values. Sherrington et al. [24], in their systematic review and meta-analysis, demonstrated that a high dose of exercise, particularly involving balance training, can prevent falls in older people. In a more recent meta-analysis [57], the same group showed that exercise reduced the rate of falls in community-dwelling older people by 21%, and had a fall-prevention effect in community-dwelling people with Parkinson’s disease or cognitive impairment. In contrast to these studies, we evaluated as outcomes not only the rate of falls or number of fallers, but also the clinical scores for dynamic and static balance, participants’ fear of falling, physical performance,

and quality of life in order to analyze the improvements in performing daily activities with less risk and fear of falling. Moreover, we focused on elderly people without neurological or cardiovascular disease, to recommend PE as an effective treatment for all the elderly population which could prevent impairment of muscle strength and a higher likelihood of falling. Furthermore, we analyzed various kinds of specific BT programs, including aquatic exercise, which could represent valid alternative or complementary activity to land-based exercise.

5. Conclusions

This systematic review proved that physical exercise is an effective treatment to improve static and dynamic balance and reduce the number of falls and fallers for patients aged 65 or over. The meta-analysis reports strong evidence that exercise programs can reduce fall rates in the geriatric population. Balance and postural exercises should be included in training protocols for the elderly in order to prevent the risk of falls, and they should be performed in the entire healthy population, not only as rehabilitation after stroke, fractures, or for patients affected by neurodegenerative disease. However, further large-scale trials with longer follow-up are needed to estimate the long-term effects of balance programs on decreasing the rate of falls. Moreover, more studies involving aquatic exercise or comparing aquatic versus land-based programs are necessary to promote innovative strategies to prevent falls in older people, which can be delivered by exercise trainers.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2077-0383/9/8/2595/s1>, Table S1: PRISMA Checklist.

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Review

Family Caregiver Strain and Challenges When Caring for Orthopedic Patients: A Systematic Review

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Abstract: Background: Caregivers represent the core of patients' care in hospital structures, in the process of care and self-care after discharge. We aim to identify the factors that affect the strain of caring for orthopedic patients and how these factors are related to the quality of life of caregivers. We also want to evaluate the role of caregivers in orthopedic disease, focusing attention on the patient-caregiver dyad. Methods: A comprehensive search on PubMed, Cochrane, CINAHL and Embase databases was conducted. This review was reported following PRISMA statement guidance. Studies were selected, according to inclusion and exclusion criteria, about patient-caregiver dyads. For quality assessment, we used the MINORS and the Cochrane Risk of BIAS assessment tool. Results: 28 studies were included in the systematic review; in these studies, 3034 dyads were analyzed. Caregivers were not always able to bear the difficulties of care. An improvement in strain was observed after behavioral interventions from health-care team members; Conclusions: The role of the caregiver can lead to a deterioration of physical, cognitive and mental conditions. The use of behavioral interventions increased quality of life, reducing the strain in caregivers of orthopedic patients. For this reason, it is important to consider the impact that orthopedic disease has on the strain of the caregiver and to address this topic.

Keywords: caregiver; orthopedic disease; caregiver strain; hip; knee; shoulder; caregiver stress; dyads

1. Introduction

Orthopedic surgery is one of the most commonly performed surgeries worldwide [1,2]. Patients undergoing orthopedic surgery can experience difficulties in the management of post-surgical symptoms and physical limitations [3]. Orthopedic patients may experience barriers such as difficulties with Activities of Daily Living (ADL) [4,5], and problems returning to post-surgical lives. For these reasons, the role of the caregiver is of paramount importance in supporting dependent people both in simple and complex activities [6]. Although they are often family members without formal training, they take part in the activities of daily care, offering emotional support to the patients and replacing, in whole or in part, the physically dependent patients in the ADLs. Additionally, they monitor the patient's care pathway, managing the symptoms and taking on the family responsibilities previously managed by the patients [7]. All these factors contribute to increasing the caregivers' workload and they could affect caregivers' quality of life, both pre to post the patients' orthopedic surgeries [8]. The poor physical conditions of patients are associated with a decrease in the quality of life of the caregiver and an increase in stressors, due to all the caregivers' responsibilities; the caregiver can also present

physical problems due to the effort involved in helping the patient to move. It is therefore important to enhance the caregiver's safety to improve his/her physical condition [9]. Caregiving is emotionally and cognitively demanding, and literature indicates that caregivers' overall health is adversely altered [10].

The term "dyad" refers to the relationship between patient and caregiver, who are involved physically and emotionally. The dyad is an important foundation for problem identification and problem-solving included in the orthopedic patient process, from the pre-operative period to the post-operative period. Humor, reassurance, and empathy are also important factors in this dyad relationship. There is a need to enhance patient-caregiver dyad research, by studying the relationship from pre-operative to follow-up to evaluate the changes in the patient's outcomes, but also in the caregiver's psychological and cognitive sphere. There is a need to identify the type of supportive relationship that is established with informal caregivers to offer them an appropriate educational plan. Furthermore, it is necessary to evaluate if the degree of instruction received during the hospitalization period and the knowledge of informal caregivers about the disease, is sufficient for them to be able to face a functional recovery process in the postoperative period in order to maintain the role of caregiver after patients' surgery [11].

The present systematic review aims to identify, analyze and synthesize the studies on the role of informal caregivers' strain and difficulties when caring for orthopedic patients, focusing attention on the patient-caregiver dyad, during the pre-operative to post-operative period.

2. Materials and Methods

A literature review was performed and reported following PRISMA statement guidance [12]. Preliminary searches of main databases could not find any existing or ongoing systematic reviews on caregiver strain or difficulties of caring for orthopedic patients.

2.1. Eligibility Criteria and Search Strategy

Key words and combinations of key words were used to search the electronic databases and were organized according to the Population Intervention Comparison Outcome (PICO) model as follows.

Study: original studies with different study designs; English language; recent studies (from 2003 to 2020).

Participants: patient-caregiver dyads, orthopedic patients and informal caregivers.

Interventions: educational interventions, home-care rehabilitations, emotional and social supports.

Outcome measures: The primary outcome of the review is the caregivers' role in the orthopedic patients' functional recovery, the caregivers' knowledge to manage orthopedic disease symptoms, the caregivers' strain, and the dyads' quality of life; the secondary outcome is the impact that orthopedic disorders have on quality of life, on stress level and on the psychological and physical status of patients.

A comprehensive search of the databases PubMed, Medline, Cochrane, CINAHL, and Embase databases was conducted since the inception of the database to March 2020 with the English language constraint. To ensure a comprehensive search, facet analysis, necessary to identify the key terms to be used in the search strategy, was carried out. Keywords were combined using the Boolean operators "AND" and "OR". The search strategy was iterative and flexible within the limits of the search engines of the individual databases.

The following medical subject heading (MeSH) keywords and free terms were used for the search: caregiver, spouse, orthopedic disease, orthopedic, caregiver burden, hip, knee, shoulder, elbow, wrist, hand, humerus, femur, patella, spine, ankle, foot, caregiver stress, patient-caregiver dyads. Search strategies were checked by two reviewers (VC and GF). The exclusion criteria included: formal caregivers, reviews, books, patients and caregivers without a relation. Further details about search strategies are in Appendix A.

2.2. Study Selection and Data Collection

Two researchers (VAr and VAI) independently reviewed all studies (title, abstract and full text) that met the inclusion criteria and extracted relevant data. Disagreements were resolved by a discussion among the reviewers.

We included observational studies, prospective studies, cohort studies, mixed studies, pre–post quasi-experimental designs, randomized controlled trials, descriptive cross-sectional studies, prospective longitudinal cohort studies, non-randomized trials, qualitatively focused ethnographic approaches and retrospective analyses. The studies included articles published from 2003 to 2020. Disagreement regarding the exclusion and inclusion criteria were decided by the senior reviewer (VD).

2.3. Quality Assessment

Two reviewers independently evaluated (VAr/VAI) the potential risk of bias of the studies included using MINORS [13], a methodological index for non-randomized studies, and the Cochrane Risk of Bias Tool [14] for randomized controlled trials.

The MINORS items were scored as 0 if not reported, 1 when reported but inadequate, 2 when reported and adequate. The global ideal score was 16 for non-comparative studies and 24 for comparative studies.

The Cochrane Risk of Bias Tool assessed randomized controlled trials with the following criteria: selection, performance, detection, attrition, reporting and other biases. Each criterion was evaluated assigning zero for low risk, one point for unclear risk, and two points for high risk of bias. The potential total score range was 0–14, in which a low score indicated a higher quality level, and a high score indicated lower quality. Based on this score, an overall score of 0–1 shows high quality, an overall score of 2–3 shows moderate quality, and an overall score of >3 shows low quality [15].

2.4. Data Synthesis and Analysis

Data were extracted and synthesized through Microsoft Excel. Several data were extracted, and they concern outcome measures; authors and year; study design; orthopedic disease; aim of each study follow-up period; the relationship between patient and caregiver; number of patients and caregivers for each study; data findings; and study conclusion.

Data analysis was done using the description of the study and patient and intervention characteristics. Categorical variable data were reported as percentage frequencies. Continuous variable data were reported as mean values, with the range between the minimum and maximum values.

3. Results

The selection process is illustrated in Figure 1. The search strategy yielded 61 articles. After duplicate removal and title, abstract and full texts review, 28 studies were evaluated for methodological quality and were eligible for the review.

3.1. Study and Patient Characteristics

A total of 3034 patients–caregiver dyads were reviewed (Table 1).

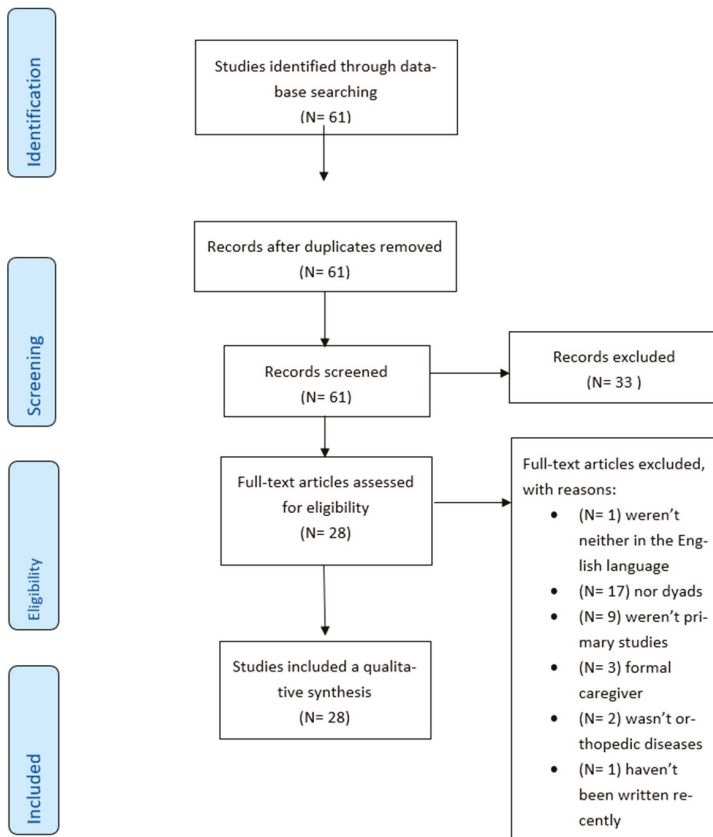


Figure 1. Study selection process and screening according to the PRISMA flow chart [12].

According to the aim of the review, the studies included analyzed the patient–caregiver dyad in the orthopedic disease context. It was found that the majority of the studies included (75%) analyzed dyad characteristics in hip disease (hip fracture, hip arthroplasty, hip deformity). To a lesser extent, 11% of the studies considered patients affected by knee orthopedic disease (knee fracture, knee arthroplasty, patella fracture) and 14.3% with backbone conditions (spinal arthrodesis, scoliosis, spine deformity, and cord injury) (Table 2).

Table 1. Characteristics of included studies: author and country; number of patients; number of caregivers; outcome measures; follow-up; data findings; conclusion; relationship with the patients.

Author and Country; Number of Patients; Number of Caregivers	Outcomes Measures; Follow-up	Outcome Measures *; Follow-up	Relationship with the Patients
Shen, 2015, China [13]; 492; 539.	FES-I ($p < 0.001$); FRS ($p < 0.001$); VAS 24 months	75.4% of family caregiver and 70.7% of patients showed FOF; Regular follow-up examinations showed a lower family caregiver FES-I score and a higher patient FRS.	321 spouses (59.5%), 171 (31.7%) offsprings
Patrocinio Ariza-Vega, 2019, Spain [14]; 172; 172.	CSI ($p < 0.001$); 1 year	High level of caregiver difficulties at the hospital, at 1 and 3 months, and at 1 year after surgery; Support and training as strategies of treatment to reduce caregivers' difficulties.	Partner/spouse 39 (23%), son 15 (8%), daughter 94 (55%), others 24 (14%)
Margaret J. Bull, 2017, US [7]; 39; 39.	CAM (Sensitivity of 94–100%, Specificity of 90–95%); FAM-CAM (Sensitivity of 87.5, Specificity of 94.2%); BSS; 3 weeks pre-surgery; 2-weeks and 2 months post-hospitalization. Caregivers: 2-days post-surgery	The caregiver rating is high on the FAM-CAM 2 days after surgery; Recognizing presence or absence of delirium symptoms by caregivers.	Spouse 24 (62%), daughter 8 (21%), others 7 (17%)
Maria Croffy, 2003, Australia [15]; 32; 66.	MBI ($p = 0.738$); TUG ($p = 0.001$) Medical Outcomes; SF-36 ($p = 0.689$); CSI ($p = 0.140$); 4 months; 12 months	Caregiver difficulty reduction is achieved by home-based therapy and rehabilitation for patients; Functionally independent patients, return home earlier, with increased involvement of caregivers.	NS
Cuicui Li, 2018, China [16]; 87; 87.	ZBI (36.83 ± 13.30); GSE (21.67 ± 7.65); 0	Social support and self-efficacy might be helpful to reduce caregivers' difficulties.	Mothers 51 (58.6%), others 36 (41.4%)
Rachel L. Difazio, 2016, US [17]; 44; 44.	CP CHILD ($p < 0.001$); ACEND ($p = 0.26$); 1 year	Children's HRQOL improved over 12 months after spinal surgery; steady improvement over time after hip surgery; decrease at 6 weeks; Caregivers reported an improvement in HRQOL 1 year after orthopedic surgery.	NS
Mohammad Hossein Ebrahinzadeh, 2013, Iran [18]; 72; 72.	SF-36 ($p < 0.001$); 6 months	Wives worked full time at home. 88.9% of veterans had a paraplegic lesion; The SF-36 scores of the spouses were lower. The caregivers' challenges can impact the QOL of caregivers.	Spouse 72 (100%)
Jacobi Elliott, 2014, Canada [19]; 8; 11.	Questionnaire; 0	Facilitators and barriers included prior health care experience, trusting relationships, and the rural setting; Effective strategies to improve information sharing and care continuity may be involved.	Adult children 6 (54.5%), spouses 2 (18.1%)

Table 1. Contd.

Author and Country; Number of Patients; Number of Caregivers	Outcomes Measures; Follow-up	Outcome Measures *; Follow-up	Relationship with the Patients
Amit Jain, 2018, US [20]; 251; 251	HRQOL ($p < 0.001$); 2 years post-surgery RNLI (33.3); CBI	HRQL: 74% of caregivers are a "lot better"; Caregiving in spinal surgery is ranked as the most beneficial intervention in the patients' lives. Caregiver burden is high at 18 and 24 months post-hip-fracture;	NS
Katherine S. McGilton, 2019, Canada [21]; 76; 76.	2 years post-hip fracture	There is a need for interventions for patients to enhance their RNLI and to support caregivers in decreasing their difficulties in caring.	Marital status, married or common-law partner 26 (34%)
Laura Churchill, 2018, GB [22]; 14; 14.	Questionnaire; 6 months Questionnaire;	Concerns and challenges are mobility, pain, self-care and caregiver support; Outpatient THA can be implemented with pre-operative education, clarification of recovery processes and expectations. More details are needed from care providers to self-manage symptoms.	NS
Odom-Forren J, 2017, US [3]; 9; 10.	2 weeks after surgery	Nurses should be focused on preparing patients to manage sustained recovery issues at home.	Spouses 7 (70%), parents 2 (20%)
Jung-Ah Lee, 2014, US [11]; 30; 30.	Questionnaire; At hospitalization	Patients and caregivers take daily injections of heparin. Patients with hip fracture and their caregivers may need further VTE preventive education.	child or son/daughter-in-law 19 (63.4%), 3 (10%) spouses
Pi-Chu Lin, 2007, Taiwan [23]; 95; 95.	OMFAQ; SERS; FOS; FFRS; FRS; CBI; 1 week and 1 month after discharge	1 week after hospital discharge the patients' physical functioning, self-efficacy, and social support contributed to variance in caregivers' difficulties; A health education and social support program should be designed to improve the primary caregiver's knowledge and to reduce the burden of care.	Apouses 30 (31.6%), sons 20 (21.1%), 18 (18.9%) daughters, 17 daughters-in-law (17.9%), grandchildren 7 (7.4%)
Hsin-Yun Liu, 2015, Taiwan [24]; 276; 276.	CBI; CMMSE; PS; MICROFET2; MNA; SF-36; 1-3-6-12 months after discharge	MCS levels were lower (22.4%), moderate (34.1%) and highest (43.5%); Health care providers could consider family caregivers' mental well-being while estimating recovery times and health outcomes of patients.	Spouse 70 (25.3%), son 61 (22.1%), daughter 57 (20.6%), daughter-in-law 71 (25.7%), other 17 (6.1%)

Table 1. Contd.

Author and Country; Number of Patients; Number of Caregivers	Outcomes Measures; Follow-up	Outcome Measures *; Follow-up	Relationship with the Patients
Asha Manohar, 2014, US [25]; 44; 44.	Questionnaire: ADL; Post-operative days; 0-3-7-30	Many patients needed more time to resume their ADL. Primary caregivers' disturbances were emotional and physical; Informal caregiving may be an unrecognized physical and psychological burden and may have a significant societal impact.	NS
Mariana Ortiz-Piña, 2019, Spain [26]; 70; 70.	FIM; Euro-Qol/EQ-5D; TUG; CBZl; SPPB; 4 weeks and 12 weeks after discharge	70 patients with a high pre-fracture functional level were allocated into a tele-rehabilitation group; Telerehabilitation is an option to promote recovery of the pre-fracture functional level.	NS
Mashfiqul A Siddiqui, 2010, Singapore [27]; 76; 76	CSI; 6 months	To 1 week of admission, and at 6 months, the caregivers were stressed. The stress factor was a financial strain. Adequate resources should be available to caregivers of patients with osteoporotic hip fractures.	NS
Benedict U. Nwachukwu, 2019, NS [28]; 95; 95.	UCLA Activity Score; HRQoL; Rehabilitation; 2 years post-surgery	Active adolescents assigned higher utility to achieve a stable return to the same function and lower utility to health states in which they were not fully participating in sport; These findings provide insight into the health-related quality of life impact for acute patella dislocations and their management.	NS
Joshua A. Parry, 2019, NS [29]; 29; 29.	CBI; DS 6 months	Caregivers have negative effects on their finances, relationships, work hours, or intent to place the patient in a care facility. Caregivers with high caregiver burdens were more likely to consider the placement of the patient into a long-term care facility.	NS
Sara Elli, 2018, Italy [30]; 147; 147.	BRASS; At the beginning of the rehabilitation program	The caregivers assign lower scores than the doctor; Caregivers' altered perceptions can lead to a general lack of satisfaction with the outcome at the end of the rehabilitation process.	NS
Yea-Ing Lotus Shyu, 2012, Taiwan [31]; 135; 151.	PRS; MOS; SF-36; CBI; 1-3-6-12 months after discharge	Caregivers' mental health was lower at 12 and 1 month after discharge; The home care nurses should develop interventions early after discharge.	1/3 sons (32.66%), daughters-in-law (26.7%), spouses (20%), daughters (14.1%).

Table 1. *Cont.*

Author and Country; Number of Patients; Number of Caregivers	Outcomes Measures; Follow-up	Outcome Measures *; Follow-up	Relationship with the Patients
Åsa Johansson Stark, 2016, Finland [32]; 306; 306.	During recovery	If nurses gave information to partners, they experienced a greater quality of recovery; Spouses' emotional state is important in the patients' quality of recovery.	Spouses 306 (100%).
Justine Toscan, 2012, Canada [33]; 6; 6.	Questionnaire; During transition care	Four factors related to illness were confusion, unclear roles and responsibilities, diluted personal ownership over care, and role strain; Supports the notion of collaborative practice and includes an appropriate, informed role for patients and informal caregivers.	Children 5 (99%)
Cornelis L. P. van de Ree, 2017, Netherlands [34]; 123; 123.	CarerQoL; 7D score; 1-3-6 months	The average amount of informal care provided per patient per week was 39.5 during the first six months; The Carer QoL was not associated with the intensity of the provided informal care.	Partners (44.7%), child (43.1%), sibling (5.7%), others (6.5%)
Li-Chu Wu, 2013, Taiwan [35]; 116; 116.	Questionnaire; 1 month after discharge	Impairments in physical functions were standing up/sitting down and dressing. The care needs were wound care, medical visits, cleaning, maintaining living; The physical function status was improved 1 week and after 1 month after discharge. The care needs and the difficulty of tasks for caregivers were negatively related to physical functional status.	Daughters or Sons (54.3%), Spouses (34.5%), Foreign workers (11.0%).
Jayson D. Zadzilka, 2018, US [36]; 150; 150.	CSI; KOOS; 4 weeks and 1 year after surgery	CSI scores at 1 year were lower; The caregivers' difficulties were high in the early post-operative period. It was close to zero by one year post-operation.	NS

ACEND: Assessment of Caregiver Experience with Neuromuscular Disease; BRASS: Braylock Risk Assessment Screening Score; BSS: Bakas Satisfaction Scale; Carer QoL 7D Score; Carer Quality of Life 7D Score; CAM: Confusion Assessment Method; CBI: Chinese Barthel Index; CBS: Caregiver Burden Rating Scale; CBZ: Caregiver Burden Zarit Intervention; CMMSE: Chinese Mini Mental Status Examination; CPCHILD: Cerebral Palsy Child; CSI: Caregiver Strain Index; DS: Depression Scale; EQoL-5D: Euro Quality of Life 5D; FAM-CAM: Family Confusion Assessment Method; FES-I: Falls Efficacy Scale-International; FRRS: Family Function Rating Scale; FIM: Functional Independence Measure; FOS: Filial Obligation Scale; GSE: General Self-Efficacy Scale; HADS: The Hospital Anxiety and Depression Scale; HRQoL: Health Related Quality of Life; HSS-Pedi-FABS: Hospital for Special Surgery Pediatric Functional Activity Brief Scale; IFS: International Fitness Scale; IADL: Instrumental Activities of Daily Living; KESo: Knowledge Expectations of Significant Other; KOOS: Knee Injury and Osteoarthritis Outcome Score; MBI: Maslach Burnout Inventory; MCI: Mild Cognitive Impairment; MICRO FET2: Micro Force Evaluation Testing 2; MNA: Mini Nutritional Assessment; MOS: Medical Outcome Study; MOS SF-36: Medical Outcome Study Short Form-36; OMAFQ: Multidimensional Functional Assessment Questionnaire; PPS: Performance Related Scale; PS: Pain Scale; QoL: Quality of Life; RKso: Received Knowledge of Significant Other; RNLF: Reintegration to Normal Living Index; SERS: Self Efficacy Rating Scale; SFES-I: Short Falls Efficacy Scale-International; SF-36: Short Form 36; SPPB: Short Physical Performance Battery; TUG: Timed Up and Go Test; UCLA: University of California, Los Angeles Loneliness Scale; VAS: Visual Analog Scale; VTE: Venous Thromboembolism; ZBI: Zarit Burden Interview.

Table 2. Characteristics of orthopedic diseases in included studies.

JOINTS			TOT *	%
Hip	Hip fracture	19	21	75%
	Hip arthroplasty	1		
	Hip deformity	1		
Backbone	Spinal arthrodesis	1	4	14.3%
	Scoliosis	1		
	Spine deformity	1		
	Cord injury	1		
Knee	Knee fracture	1	3	10.7%
	Knee arthroplasty	1		
	Patella fracture	1		

* TOT: Total.

The topics of the studies included in the systematic review make it possible to evaluate the caregiver’s role in the orthopedic patients’ functional recovery, dealing with knowledge to manage symptoms and orthopedic disease in 8 studies, caregiver strain in 15 studies and dyads’ quality of life in 5 studies.

In the studies evaluating the quality of life of the dyad, 7.14% of the studies affirmed that the patient’s quality of life was improved due to the assistance provided by the informal caregiver. Despite the improvement in patients’ quality of life, their quality of functional recovery does not improve, and the 14.2% of studies state that it is influenced by caregivers’ psychological factors.

Regarding the caregivers’ quality of life, 7.14% of the studies say the decrease in caregivers’ quality of life is related to the increasing intensity of care and caregiver strain [14].

The studies analyzing caregiver strain report that the factors affecting caregiver difficulties are increased recovery time (21.4%), complication and symptom management (14.2%), financial resources (10.7%), functional level reduction (10.7%), bad healthcare experiences (7%), any trusting relationships (7%), patients’ and caregivers’ age (7%), poor social support (7%), poor self-efficacy (7%), transport (3.5%), and rural environment (3.5%). Two studies identified a significant correlation between caregiver strain and caregiver characteristics such as age [16,17] and gender [17].

The studies included in the review used some different follow-up periods: the pre-operative period (12.5%) and 2 weeks (4.6%), 1 month (18.2%), 3 months (20.4%), 6 months (23.3%), and 1 year (21%) after surgery. The follow-up period analysis was useful for analyzing the caregivers’ strain duration. In studies that analyzed the duration of caregiver strain, fourteen percent of studies reported that caregiver strain lasted for one year, 10.7% for six months, 7.1% for one month and 3.5% for two years.

Regarding the studies that analyzed knowledge to manage symptoms, they reported that pre-operative education was fundamental to improve the management of symptoms. Pre-operative education and postoperative social support reduced caregiver strain in 46.5% of studies.

To understand the relationship between the informal caregivers and the patients that form the dyads, studies reported that the major of informal caregivers were patients’ relatives. The most common relationships between the primary caregiver and the care recipient in this review included spouses (22.1%), daughters (8.7%), sons (6.7%), daughters-in-law (5.2%), and others, including partners, mothers, grandchildren and siblings (9.2%) (Table 3).

Table 3. Caregivers’ demographic characteristics (relationship with patients).

Relationship with Patients	N	%
SPOUSE	726	23.9%
CHILDREN (DAUGHTERS AND SONS)	468	15.4%
OTHERS	162	5.3%
DAUGHTER IN LAW	160	5.2%
MOTHERS	51	1.7%
GRANDCHILDREN	25	0.8%
SIBLING	7	0.2%
TOTAL	1599	52.7%
N/A	1435	47.2%

3.2. Intervention Characteristics

The most common outcome measures observed in original studies according with the aim of this review were Caregiver Strain Index (CSI), utilized in 32% of the studies recruited [18–25]; Zarit Burden Interview (ZBI), in 7.14% [26,27]; Mini-Mental Test (M-MT) in 7.14% [22,27]; and Health-Related Quality of Life score (HRQL) in 14.2% of the studies [27–30].

Participants’ knowledge of the intervention and post-surgical management was tested via Knowledge Expectations of significant others (KEso) and Received Knowledge of significant others (RKso) [16]; confusion assessment method (CAM) and family version (FAM-CAM) [7] were used to measure empowering by knowledge.

Measures for general health status included the Short Form 36 Health Survey (SF-36) [18,22,31,32], the Functional Independence Measure Score (FIM) [27]; the Short Physical Performance Battery (SPPB) [27]; Time Up and Go Test (TUG) [18,19,27]; International Fitness Scale (FIS) [27]; The University of California, Los Angeles Activity Scale (UCLA) [29]; The Blaylock Risk Assessment Screening Score (BRASS) [37]; and the italics Self-Efficacy Scale (GSE) [21,26].

ADLs for patients and caregivers were assessed using the Barthel index [18,22,32]; the Reintegration to Normal Living Index (RNLI) [20]; and the Family Function Rating Scale [21]. The Visual Analogue Scale for Pain (VAS) [27,33] was the scale most often used to evaluate symptoms, as well as depression scales [24,27].

3.3. Quality Assessment

Most of studies included in this review (N = 27; 96.4%) were evaluated with MINORS. Of these, one study (3.57%) had low risk of bias and 26 (92.8%) had high risk of bias. The only RCT (Crotty, 2003) in this review had moderate quality due to insufficient details about the double-blinding procedure.

4. Discussion

This review aimed to synthesize the studies on the role of informal caregiver strain and difficulties when caring for orthopedic patients, focusing attention on the patient–caregiver dyad, from the pre-operative period to the post-operative period. Family caregivers are a relatively unused resource as a way to identify early symptoms and complications in orthopedic patients and to improve health outcomes for orthopedic patients. When pre-operative education is performed, family caregivers can apply their knowledge by acting on early recognition of symptoms [3,7].

Learning about diseases drives caregivers to satisfaction and to learn strategies to help patients, also with emotional support. Extensive efforts have been made to understand the strain felt by caregivers of patients with orthopedic disease. Orthopedic caregivers without enough information had

less security in dealing with the patients' disease than those who received an appropriate education from health care team members: this is a finding that was consistent with the stress and coping model of caregiving [29].

Caregiving and poor quality of life can relate bidirectionally. In the dyad, concerns are about mobility, pain, self-care, support from the caregiver and discharge on the same day regarding recovery expectations, and drugs and their effect on postoperative recovery [34]. Orthopedic patients feel more pain and greater difficulties with physical activity; this leads to an increase in the caregiver's workload, and several studies underestimate this result [35]. The impact of the orthopedic disease on dyads is crucial for patients' outcomes and caregiver strain. The physical outcomes of patients and their functional recovery, and also the impact of caregiver assistance on care transition, have been studied more frequently [36].

In this context, the formal rehabilitation program has a key role in restoring patient autonomy and also involving the caregiver to reduce and improve rehabilitation times [38,39]. When the patients' formal post-surgery rehabilitation program is insufficient, the supply of a family caregiver is fundamental. For example, it could be necessary to improve the information and caregivers' education about the management of symptoms. A focus on the orthopedic patient and caregiver education regarding the clinical post-operative problems, potential risks involved, and patient and caregiver roles to improve the caring process is necessary.

In many of the studies recruited, caregiver strain is one of the main topics. The difficulty of assistance is often not recognized, and it can lead to mental and physical problems, but can also have a strong impact on social life [35]. Caregiver stress increases in the immediate postoperative period, while decreasing a lot after a year after surgery [25]. Especially in patients undergoing hip replacement, the caregiver strain is very high, which is why it is important to ease caregiver stress and increase the quality of care throughout the functional recovery period, including the periodic follow-up [24]. In most of the studies analyzed, the follow-up period of the dyad is approximately one year. This means that it cannot be said that the interventions implemented on the dyad provide long-term benefits and that the outcomes are valid.

Concerning the strain of care [30], we have found that caregivers showed disorders in the cognitive and physical spheres of their daily lives during the treatment period, from the pre-operative to post-operative period, leading to a reduction in their quality of life.

This review showed the importance of information and education before and after orthopedic surgery, to limit the functional restriction of patients by scared caregivers and to analyze its influence on functional recovery. The patient's functional level, quality of life, physical performance, pain, caregiver strain, and their the emotional and cognitive state should be evaluated, and perception of physical state should be assessed [40]. A study conducted in 2010 aimed to investigate the causes of stress attributed to the caregivers of patients with orthopedic disease [23]. The caregiver tension can result from changes in the patient's physical and cognitive states, and the sustained role during the patient's daily life activities. Several factors can contribute to caregiver stress, including financial strain, which is one of the most significant causes of caregiver stress. The financial problems arise from the need to incur medical expenses, rehabilitation, and transportation. This can be added to the physical and mental stress of the caregiver.

Post-operative recovery of patients was associated with the mental state of their family members. When a caregiver's mental state is "poor", the patient is more likely to relapse, which could lead a prolongation of recovery. Agreeing with this hypothesis, it is recommended to consider the mental well-being of the informal carers by evaluating patient recovery time [22].

The patient-caregiver dyad has also been studied in the traumatological and chronic fields. It has been well documented in hip injuries, while less attention is paid to other orthopedic conditions. Quantitatively, 19 studies deal with hip fractures, four studies deal with knee injuries, five studies with spine injuries, and two studies with general orthopedic pathologies. All revised studies refer to the caregiver strain and the amount of care for the patient with the orthopedic condition, which will

reduce the quality of life of the caregiver due to the resulting growing stress. Many studies focus on patient outcomes related to care by a caregiver. The aim is to improve care but also to reduce the strain and stress factors attributable to this type of relationship established with the patient.

The present results should be interpreted in the context of the strengths and weaknesses of the studies composing the orthopedic caregiver. For example, most studies of orthopedic caregivers have used self-report questionnaires rather than assess the level of quality of life or have used rating scales that emphasize increasing caregiver strain.

Self-reported quality of life was greater than objective measures of quality of life, so it is possible that the actual caregivers' stress level was even worse than that estimated by the present systematic review. Repeating objective measures for all the caregivers would yield more accurate estimates of the real caregiver strain when caring for orthopedic patients.

Caregivers could be important to patients' healthcare, particularly according to the duration of caregiving, workload and stress level: these are also the factors that increase caregiver difficulties. Patients demonstrated the greatest increase in quality of recovery thanks to communication with their caregiver and thanks to the help they received from caregivers in maintaining social interaction. Besides, caregivers could improve orthopedic patients' life with behavioral interventions such as emotional comfort and support, both during pre-operative and post-operative periods.

Limitations

There were several limitations to this study. Further research is needed to examine how the intervention described would be successful with a larger sample. The study lacked a control group: future research is needed using a design that randomly assigns participants to intervention and control groups. Despite these limitations, the interventions were successful in increasing knowledge of caregivers' importance in orthopedic disease.

5. Conclusions

Despite the challenges in studying the role of caregivers in orthopedic diseases and family caregiver strain and challenges when caring for orthopedic patients, the literature indicates that not only the increase in caregivers' stress levels but also the decrease in quality of life was less severe in caregivers who received appropriate behavioral interventions including health care advice, such as medication advice or psychological tips. To improve the quality of health care, stressors should be considered for caregivers due to the high strain, especially in the post-discharge period.

Clinicians should consider the importance of caregiver interventions, not only for the orthopedic patient but also for the spouse, child, or friend who will be providing care for that individual. Further studies should focus on the important physical and mental role of the informal caregiver for patients who receive orthopedic surgery and the importance of psychological sphere for the patient-caregiver dyad. Focusing on caregivers' welfare rather than only on patient well-being could radically improve both caregivers' performance and patients' recovery.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. List of Search Terms Used for Systematic Review

Search terms for Medline Complete (via EBSCO Host): 1971 to 27 January 2019

1. MH "Chronic Disease"
2. chronic disease*
3. chronic illness*
4. chronically Ill
5. 1 or 2 or 3 or 4
6. MH "Aged+"
7. Aged
8. Elderly
9. older adults
10. 6 or 7 or 8 or 9
11. MH "Continuity of Patient Care+"
12. continuity of patient care
13. patient care continuity
14. continuum of care
15. continuity of care
16. care continuity
17. 11 or 12 or 13 or 14 or 15 or 16
18. MH "Patient Readmission"
19. re-admission*
20. readmission*
21. patient readmission*
22. hospital readmission*
23. post discharge*
24. postdischarge*
25. re-hospitalization
26. rehospitalization
27. re-admit*
28. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 5 and 10 and 17 and 28

269. records found

Search terms for PubMed: 1971 to 27 January 2019

1. Chronic Disease [Mesh]
2. chronic disease*
3. chronic illness*
4. chronically ill
5. 1 or 2 or 3 or 4
6. Aged [Mesh]
7. aged
8. elderly
9. older adult
10. 6 or 7 or 8 or 9
11. Continuity of Patient Care"[Mesh]
12. patient care continuity

13. continuum of care
14. care continuity
15. 11 or 12 or 13 or 14
16. Patient Readmission"[Mesh]
17. re-admission*
18. readmission*
19. patient readmission*
20. hospital readmission*
21. post discharge*
22. postdischarge*
23. re-hospitalization
24. rehospitalization
25. re-admit*
26. readmit*
27. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 5 and 10 and 15 and 27

233. records found

Search terms for CINHAL (via EBSCO Host): 1995 to 27 January 2019

1. MH "Chronic Disease"
2. chronic disease*
3. chronic illness*
4. chronically Ill
5. 1 or 2 or 3 or 4
6. MH "Aged"
7. aged
8. older adult*
9. 6 or 7 or 8 or 9
10. MH "Continuity of Patient Care"
11. patient care continuity
12. continuum of care
13. continuity of care
14. care continuity
15. 10 or 11 or 12 or 13 or 14
16. MH "Readmission"
17. re-admission*
18. readmission*
19. patient readmission*
20. hospital readmission*
21. post discharge*
22. postdischarge*
23. re-hospitalization
24. rehospitalization

25. re-admit*
26. readmit*
27. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 5 and 9 and 15 and 27

169. records found

Search terms for Embase: 1971 to 27 January 2019

1. 'chronic disease'/exp
2. 'chronic disease'
3. 'chronic illness'/exp
4. 'chronic illness'
5. 1 or 2 or 3 or 4
6. AND 'aged'/exp
7. 'aged'
8. 'aged patient'/exp
9. 'aged patient'
10. 'aged people'/exp
11. 'aged people'
12. 'aged person'/exp
13. 'aged person'
14. 'aged subject'/exp
15. 'aged subject'
16. 'elderly'/exp
17. 'elderly'
18. 'elderly patient'/exp
19. 'elderly patient'
20. 'elderly people'/exp
21. 'elderly people'
22. 'elderly person'/exp
23. 'elderly person'
24. 'elderly subject'/exp
25. 'elderly subject'
26. 'senior citizen'/exp
27. 'senior citizen'
28. 'senium'/exp
29. 'senium'
30. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 'advance care planning'/exp
32. 'advance care planning'
33. 'care, continuity of'/exp
34. 'care, continuity of'
35. 'continuity of patient care'/exp
36. 'continuity of patient care'
37. 'episode of care'/exp

38. 'episode of care'
39. 'night care'/exp
40. 'night care'
41. 'patient care'/exp
42. 'patient care'
43. 'patient care management'/exp
44. 'patient care management'
45. 'patient care team'/exp
46. 'patient care team'
47. 'patient centered care'/exp
48. 'patient centered care'
49. 'patient helper'/exp
50. 'patient helper'
51. 'patient isolation'/exp
52. 'patient isolation'
53. 'patient management'/exp
54. 'patient management'
55. 'patient navigation'/exp
56. 'patient navigation'
57. 'patient-centered care'/exp
58. 'patient-centered care'
59. 'continuity of care'/exp
60. 'continuity of care'
61. 'continuum of care'
62. 'care continuity'
63. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62
64. 'hospital readmission'/exp
65. 'hospital readmission'
66. 'patient readmission'/exp
67. 'patient readmission'
68. 'readmission'/exp
69. 'readmission'
70. 'readmission rate'/exp
71. 'readmission rate'
72. 'readmissions'/exp
73. 'readmissions'
74. 'rehospitalization'/exp
75. 'rehospitalization'
76. 'post discharge'
77. 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
78. 5 and 29 and 61 and 75

135. records found

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