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Tesi di laurea:

THE IMPACT OF PHYSICAL EXERCISE IN THE MANAGEMENT OF RHEUMATIC DISEASES: A FEASIBILITY PILOT STUDY.

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ABSTRACT

The role of physical exercise in reducing inflammation in chronic diseases is well-documented in the scientific literature. Furthermore, some studies, suggest that physical exercise may also reduce systemic chronic inflammation levels in rheumatic diseases. The project, titled “Tapering of therapy: the Impact of LifesTyle and predictors of sustained remission (TILT study)”, aims to investigate the anti-inflammatory effects of physical exercise and dietary therapy in patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA) who are candidates for tapering biological and targeted synthetic disease-modifying antirheumatic drugs. TILT study is primarily focused on the anti-inflammatory effects of exercise, but this thesis is just focused on the outcomes of the first mesocycle of the protocol, representing a feasibility pilot-study preceding the whole project. The current analysis is focused on the effects of flexibility, aerobic, and strength training on quality of life, muscular strength, aerobic capacity, balance, flexibility, and pain management. The study was conducted on the first four enrolled participants, each with a different rheumatic disease: one with RA, one with psoriatic arthritis (PsA), and two with Ankylosing Spondylitis (AS). However, for scheduling problems only two of these patients completed the first mesocycle of physical exercise, allowing for a pre- and post-comparison of results for these individuals. Additionally, a comparison was made across all four subjects to analyze the outcomes of the pre-test. The physical exercise plan was designed in accordance with literature guidelines, focused on the particular limitations belonging to RA, PsA and AS. The first mesocycle, was composed by 10 workout sessions, prioritizing initial patient conditioning, pain management and making the patient aware about the difference between the pathological pain and the muscle soreness that can follow physical exercise. Therefore, a multimodality exercise program was provided. All four participants were male, with an average age of 48 years, an average height of 182 cm, and an average weight of 84,5 kg. Participants showed normal or mildly reduced functional capacity, with significant abnormalities were observed among the four patients. In the Senior Fitness Battery, all participants showed similar results in the strength and endurance tests, as they were generally inactive or only minimally active, with the exception of one of them. However, flexibility assessments revealed that two patients had poorer mobility in the back scratch and sit and reach tests, whereas the other two patients exhibited better outcomes in these components. All subjects achieved the maximum score in each component of the SPPB, resulting in a perfect total score. Lower-limbs strength and

power varied significantly among the subjects, probably due to differences in body weight age and physical activity levels. Grip strength, assessed using the handgrip test, showed no significant differences among the subjects. IPAQ questionaries highlighted that one patient was very active, but the others were not sufficiently active. For the two patients that completed the first mesocycle most functional evaluation parameters improved, with the exception of the 8-Foot Up & Go test. Strength and power gains were observed in knee flexors and extensors muscles with isokinetic tests. Additionally, participants showed improvements in ankle plantar and hip flexion. Finally, a reduction in pain was detected, especially in one patient who showed both acute and chronic improvements. In conclusion, it seems that a physical exercise program based on a comprehensive functional evaluation is safe, feasible and effective in patients with rheumatological diseases.

ABSTRACT (ITALIAN)

Il ruolo dell'esercizio fisico nel ridurre l'infiammazione nelle patologie croniche è ampiamente documentato in letteratura. Alcuni studi riportano, inoltre, questo effetto anche nelle patologie reumatiche. Il progetto intitolato "Tapering of therapy: the Impact of LifesTyle and predictors of sustained remission (TILT study)" ha lo scopo di indagare l'effetto antinfiammatorio dell'esercizio fisico e della dieta in pazienti con artrite reumatoide (RA) e spondiloentesoartriti (SpA) i quali sono candidati al tapering dei farmaci biologici e "targeted synthetic disease-modifying antirheumatic drugs". Lo studio TILT si concentra sull'effetto antinfiammatorio dell'esercizio fisico, mentre questa tesi riporta solo i risultati del primo mesociclo del protocollo di allenamento, rappresentando uno studio pilota di fattibilità che precede l'intero progetto. La suddetta analisi è focalizzata sugli effetti dell'allenamento aerobico, di forza e di flessibilità sulla qualità della vita, forza muscolare, capacità aerobica, equilibrio, flessibilità e sulla gestione del dolore. Lo studio è stato condotto sui primi quattro partecipanti inclusi nello studio, dei quali ognuno presentava una diversa patologia reumatica: un paziente l'RA, uno l'artrite psoriasica (PsA) e gli altri due la spondilite anchilosante (AS). Tuttavia, a causa di problemi gestionali, solo due di questi pazienti hanno completato il primo mesociclo di allenamento permettendo, quindi, un confronto pre- post- allenamento dei parametri dei test funzionali. Il protocollo di esercizio è stato realizzato seguendo le linee guida riportate nella letteratura scientifica, ponendo particolare attenzione alle limitazioni specifiche di RA, PsA e AS. Il primo mesociclo di allenamento era composto da 10 sessioni e concentrato sul condizionamento iniziale del

paziente, sulla gestione del dolore e con particolare attenzione alla consapevolezza del soggetto e alla capacità di distinguere il dolore reumatologico da quello post-esercizio. Di conseguenza, è stato proposto un protocollo di esercizio multimodale. Tutti i quattro partecipanti erano maschi, con un'età media di 48 anni, un'altezza media di 182 cm ed un peso medio di 84,5 kg. I soggetti hanno mostrato una capacità funzionale normale o leggermente ridotta, senza particolari anormalità in nessuno di essi. Nel test "Senior Fitness Battery" tutti i partecipanti hanno mostrato simili risultati nei test di forza e resistenza, poiché, ad eccezione di uno di essi, erano tutti inattivi o leggermente attivi. Tuttavia, i test di flessibilità hanno evidenziato che due pazienti presentavano una scarsa mobilità nei test "back scratch" e "sit and reach", mentre gli altri due hanno mostrato dei buoni risultati in questi test. Nel test SPPB tutti i partecipanti hanno performato perfettamente ottenendo il massimo del punteggio in tutte le componenti di esso. La variabilità in termini di forza e potenza degli arti inferiori è risultata significativa, probabilmente a causa delle differenze di peso, età e livello di allenamento nei vari soggetti. La forza della presa, invece, non ha presentato una grossa variabilità tra i soggetti ed è stata misurata tramite il test hand grip. Il questionario IPAQ ha evidenziato il fatto che uno dei soggetti era molto attivo, a differenza degli altri che erano inattivi o non sufficientemente attivi. Nei due pazienti che hanno concluso il primo mesociclo di allenamento la maggior parte dei parametri funzionali è migliorata, con eccezione del test "8-Foot Up & Go". Un incremento di forza e potenza negli estensori e flessori di ginocchio è stato osservato durante il test isocinetico. Inoltre, un aumento di flessione plantare e dell'anca è stato riscontrato. Infine, i partecipanti, in particolare uno di essi, hanno riportato una diminuzione del dolore sia in acuto che in cronico. In conclusione, sembrerebbe che un protocollo di esercizio adattato, dopo una corretta valutazione funzionale, sia sicuro, fattibile ed efficace nei pazienti con patologie reumatiche.

INTRODUCTION

Rheumatic diseases are a bunch of disorders characterized by chronic pain and inflammation affecting the joints, muscles, and connective tissues. The most common rheumatic diseases such as rheumatoid arthritis, osteoarthritis, lupus, and ankylosing spondylitis impact millions of individuals worldwide and they often lead to significant physical limitations, decreased quality of life, and increased healthcare utilization. The main focus for managing the rheumatic diseases are the pharmacological treatments aimed at reducing pain and controlling inflammation. However, there is growing recognition of the importance of a more holistic approach that includes non-pharmacological interventions such as physical exercise and dietary interventions.

Physical exercise, which includes strength training, aerobic training, flexibility and balance training, has emerged as a significant component in the management of rheumatic diseases. This thesis aims to explore the benefits of physical exercise in three types of rheumatic diseases namely Rheumatic Arthritis (RA), Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA). The thesis is built by following a study which purpose is the relationship between the physical exercise and inflammation.

1.RHEUMATIC DISEASES

Rheumatic diseases encompass a wide range of conditions. However, in this thesis, the primary focus is the effect of the exercise on three specific types of rheumatic diseases: Rheumatic Arthritis (RA), Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA). Therefore, this chapter will specifically describe these three diseases in detail.

1.1 – Rheumatoid Arthritis

1.1.1 Definition and epidemiology

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases in which chronic inflammation predominates. Inflammation is systemic, targeting articular tissues, and predisposing to cardiovascular comorbidity and increased susceptibility to infectious pathogens, resulting in a reduction of life expectancy by up to 10 years in severe cases. [1]

RA is the most frequent chronic systemic autoimmune disease with joint involvement and it affects approximately 0.5% of the adult population of Europe and North America. Females are two-to fourfold more frequently affected and predisposed to develop more severe disease manifestations. [1]

Different genetic and environmental factors are involved in the pathogenesis of disease, and they all have an influence on the risk for developing RA. The incidence rates show a considerable variation even within Europe from south to north, from 16.5 to 29 cases per million people. [2]

1.1.2 Pathogenesis

The rheumatoid synovium is a prototypic inflammatory effector site that has provided key insights into autoimmune, inflammatory, and destructive mechanisms. [3]

Synovial tissue in normal joints consists of a thin lining layer, one to three cells thick, made up of macrophages and fibroblasts, supported by a loose, vascularized connective tissue called sublining layer. In RA, the lining layer becomes hyperplastic, with both macrophages and fibroblasts proliferating, while the sublining is infiltrated by inflammatory cells. During the inflammation process, endothelial cells are activated, leading to angiogenesis and the formation of high endothelial venules. Clusters of activated dendritic cells (DCs), T cells, and inflammatory macrophages gather around blood vessels, while B cells infiltrate the synovial tissue. [1]

RA is driven by autoimmune processes involving antigen presentation by DC to autoreactive T cells and production of autoantibodies by autoreactive B cells. This process arises from the inflammatory products of macrophage and synovial fibroblast effector cells. [4] Similarly, the destructive effects of the proliferative tissue-invasive pannus, is formed by "transformed" synovial fibroblasts. [5] Additionally, bone destruction is mediated by osteoclasts, which differentiate from monocyte precursors in the tissue. [6]

Leucocyte migration in response to the inflammatory process, increases the cellularity of the synovial tissue leading to hypoxia. This results in angiogenic and cellular stress pathways, leading in tissue damage, which manifests as necrosis and apoptosis. [1]

RA synovium can be classified into distinct subtypes that are partially associated with clinical features and specific gene expression profiles. A gene expression study of RA synovial tissue identified at least two distinct subtypes. One subtype was highly inflammatory, characterized by genes related to immunoglobulins (Ig) and both innate and adaptive immunity, and was generally linked to higher clinical disease activity. The other subtype was less inflammatory, with increased expression of genes involved in tissue remodeling and repair. [7]

As mentioned previously, the development of RA is influenced by a combination of genetic and environmental factors. Indeed, the European League Against Rheumatism (EULAR) has published guidelines focusing on the preclinical and very earliest clinically apparent stages of disease. [8] This provides a framework to define the relationship between genetic, environmental, and immuno-inflammatory factors that confer the risk for AR over the time, and will uphold the development of risk stratification and prediction models in the future. [1]

Genetic factors

Disease concordance rates for twins are 15–30% (monozygotic) and 5% (dizygotic), with heritability estimates of up to 60%. [9] The major histocompatibility complex (MHC), which is highly polymorphic, contributes about one-third of this genetic susceptibility. Specific variants of the HLA-DRB gene, particularly those mapping to amino acids 70–74 of the DRβ-chains, show a strong association with RA. [10]

Although the HLA-DRB1 gene is the most critical one in RA, many other genes also contribute to the risk of developing the disease. Some of these are linked to a worse prognosis. Specific genotypes, including DRB1*04, cosegregate with distinct clinical

features including ACPA-positive, erosive disease. Genetic associations for ACPA-negative disease are distinct from ACPA positive disease, with major differences in the MHC region, including HLA-DRB1*03, as well as IRF5 and mannose-binding lectin. However, certain HLA-DRB1 alleles confer lower disease risk, and reduced radiographic progression in RA even in the presence of one copy of a susceptibility HLA-DRB1 allele, suggesting that specific subsets of MHC class II genes may confer an independent protective role. [11]

Environmental factors

Both infectious and non-infectious agents can stimulate host cells or damage mucosal sites, with particular attention to the gastrointestinal and respiratory tracts. Smoking, for example, contributes approximately 25% of the population- attributable risk of RA. Citrullination of proteins is more likely during cellular inflammation, stress, and autophagy. Whereas bronchoalveolar lavage (BAL) cells from healthy smokers contained citrullinated proteins, cells from nonsmokers did not. [12] These proteins are also found in inflamed RA joints. Environmental factors such as smoking, obesity, and exposure to toxins like silica and mineral oils may increase the expression of neoantigens through stress-induced post-translational modifications. In contrast, factors that reduce oxidative stress such as red wine, statins, and pregnancy (which promotes immune tolerance) are associated with a lower risk of developing RA. [13]

The microbial communities, or "microbiota," that colonize mammals from birth are another significant environmental factor. Although they are influenced by diet and physiology, these communities remain remarkably stable. Preclinical mouse models have defined links between segmented filamentous bacterial species in the intestine and the rapid emergence of IL-17-expressing effector T cells in the context of autoimmunity, including inflammatory arthritis. [14] Notably, a recent study found that Prevotella species, a Gram-negative anaerobe in the Bacteroides genus, are abundant in the gut of patients with early-stage RA, but not in those with established RA. [15]

1.1.3 Classification criteria and diagnosis

The accurate diagnosis of RA is challenging and remains the responsibility of the rheumatologist. Given the broad range of potential differential diagnoses and the highly variable presentation of RA, no diagnostic criteria can replace the clinical judgment and experience of the rheumatologist. It is crucial to consider differential diagnoses, including

viral polyarthritis, peripheral spondyloarthropathy, Lyme arthritis, sarcoid arthritis, other systemic rheumatic diseases, polymyalgia rheumatica, and hand osteoarthritis. [1]

Critical diagnostic features of rheumatoid arthritis

The polyarthritis onset is the most common in RA, [16] affecting primarily the proximal interphalangeal (PIP), metacarpophalangeal (MCP), and wrist joints, as well as the ankles and the metatarsophalangeal (MTP) joints. All other joints can also be affected by RA, with the exception of the distal interphalangeal (DIP) joints. Conversely, a monoarthritic onset of RA is less common, affecting larger joints, and usually evolves to typical polyarthritis that includes the small joints over time. Arthritis in RA is often accompanied by morning stiffness lasting at least 30 to 60 minutes. [1]

RFs occur in 70–80% of patients with RA. However, their utility in diagnosis is limited by their relatively poor specificity since they are found in 5–10% of healthy individuals (specially in elderly), 20–30% of those with SLE, virtually all patients with mixed cryoglobulinaemia, and many other inflammatory conditions. Antibodies to citrullinated peptides/proteins (ACPA) are usually measured by enzyme-linked immunosorbent assays (ELISA) using CCP as antigen. Anti-CCP antibodies have a similar sensitivity and specificity to RF for RA. [17, 18]

Elevations of the ESR and/or CRP level are typically seen in inflammatory conditions such as RA. Indeed, the increase in acute-phase reactants correlates with the severity of inflammation and the extent of structural damage that may develop over time. [19] Although increased levels of acute-phase reactants are not specific for RA, they are often useful for distinguishing inflammatory from non-inflammatory musculoskeletal conditions, such as osteoarthritis (OA). Therefore, elevation of acute-phase reactants was also included in the 2010 classification criteria. [1]

The 2010 classification criteria for rheumatoid arthritis

Until 2010, the classification criteria for RA in use were those by the American College of Rheumatology (ACR) dating from 1987. [20] These criteria have been increasingly debated in the recent past, because of their lack of sensitivity in early disease, due to the fact that they derived from studies in patients with long-standing, established RA. [21]

The 2010 classification criteria consist of four domains: the number and type of affected joints, serology (RF and ACPA), acute-phase reactants (CRP and ESR) and symptom duration. For classification purposes, the highest score within each domain is selected and

the four scores are then added together. The maximum possible score is 10, with a score of 6 or more indicating the presence of definitively classifiable RA. [1]

Inherent to classification criteria is the fact that they do not work in all individuals who can theoretically be tested. It is very important to understand the target population of the new classification criteria. Indeed, the 2010 criteria should be applied to any patient who presents at least one swollen joint, for which another disease is not the most likely cause. These limitations were introduced to increase the specificity of the new criteria, and to prevent patients with other diseases such as gout or SLE being tested with the criteria. [1]

About imaging techniques, like MRI and ultrasonography advance, discussions continue on how to incorporate these methods into RA classification criteria. Importantly, a clinically swollen joint is required to apply the criteria, and imaging evidence of synovitis alone is not enough. However, once clinical synovitis is confirmed, imaging can help assess the extent of arthritis and it can potentially increase the score in the “joint distribution” category of the criteria. [1]

The other important issue in imaging is the topic about the relevance of erosions. While erosions are a key outcome of RA, they are not required for classification. In rare cases of long-standing, less active RA ("burnout” disease), classification can still be made based on typical radiographic evidence, defined as erosions in more than three joints. [22]

While classification criteria aim for a good group categorization, the clinical diagnosis aims at the correct individual categorization, to minimize misdiagnosis at the individual level. Because classification and diagnostic criteria for diseases may not always place individuals in the same category, this may result in false positives or false negatives when compared to clinical diagnoses. However, this is not a flaw in the classification system, but an inherent limitation. Since classification criteria are often used by clinicians for diagnosis, it is crucial to highlight that clinicians can override classification outcomes based on their judgment. In conclusion, clinicians may diagnose unclassified patients or choose not to treat classified patients if there is no clinical diagnosis to support it. [1]

1.1.4 Clinical features

Early rheumatoid arthritis

The onset of articular symptoms is usually insidious as mono-, oligo- or polyarthritis with pain, soft tissue swelling, and sometimes warmth as a correlate of acute synovitis (Figure 1.1). The most affected joints include the metacarpophalangeal (MCP) joints, the proximal

interphalangeal (PIP) joints, wrists and forefeet, especially the metatarsophalangeal joints (MTP). For unknown reasons, the distal interphalangeal (DIP) joints are not affected. This characteristic plays a crucial role in differential diagnosis, helping to distinguish RA from PsA and OA, where the DIP joints are commonly affected. [1]

In addition to the articular manifestations such as pannus formation, joint effusion, bursitis, and risk of cartilage and bone destruction, periarticular symptoms can include tendinitis, tenosynovitis, epicondylitis, carpal tunnel syndrome, and myalgias. While involvement of shoulder and hip joints is relatively rare in early RA, it becomes more common in patients with established and late-onset disease. [1]

In relation to the severity of the local and systemic inflammatory response, the disease process can be accompanied by nonspecific symptoms such as long-lasting morning stiffness affecting the joints, generalized weakness with loss of energy, fatigue, weight loss, fever, and early functional joint impairment. [23, 24] Additionally, depression and fatigue in relation to the inflammatory process of RA can cause psychological stress and a significant reduction of quality of life. Also, high levels of disability have a negative impact on social participation and psychological functioning of patients. [1]

Established and advanced rheumatoid arthritis

In the established and advanced phases of RA, the inflammatory process in the joints leads to synovitis with pannus formation, resulting in evident signs and symptoms of arthritis. In the affected joints, the destructive nature of RA and the impact on bone metabolism manifest as periarticular bone demineralization, resulting in an irreversible destruction of both cartilage and articular bone. First erosions are frequently found at the insertion region of the joint capsule, where pannus tissue starts to invade into the naked bone structures not covered by cartilage. [1]

As signs of advanced disease in hands, the involvement of carpal bones and MCP joints causes ulnar drift, often in combination with radial deviation of the wrist and flexion deformities (Figure 1.1). Typical wrist deformities encompass volar subluxation of the hand with a visible sliding at the radiocarpal joint and radial deviation of the carpal bones (Figure 1.2). Involvement of the radioulnar joint can result in instability and dorsal subluxation of the ulnar head with a “piano key” phenomenon on downward pressure. The resulting instability and mechanical tension of the ulnar head can eventually cause rupture of carpal extensor tendons. [1]

Involvement of MCP and PIP joints is typically symmetric and can lead to articular destruction, subluxation, or dislocation and finally, to an ankylosis of joints. Tenosynovitis of tendon sheaths can cause typical finger deformities such as Z-deformity of the thumb, swan-neck deformity, and boutonnière deformity (Figures 1.1 and 1.2). Furthermore, tenosynovitis of the carpal flexor tendons can result in compression of the median nerve causing carpal tunnel syndrome. Another typical sign of established RA is atrophy of interosseous muscles of the hand mainly due to reduced use as a consequence of joint pain and stiffness. As in early RA, the DIP joints are typically not involved even in advanced stages of disease. [1]

As signs of advanced disease in the feet, involvement of the metatarsophalangeal (MTP) joint is very common, frequently leading to forefoot deformities (Figure 1.3). Synovitis with erosive bone changes as well as tenosynovitis especially of the flexor tendons can cause clawing of the toes and dorsal dislocation of the MTP joints. [1]

Another occasional but relevant manifestation of RA can affect the temporomandibular joints, resulting in pain and limitation of mouth opening. [1]

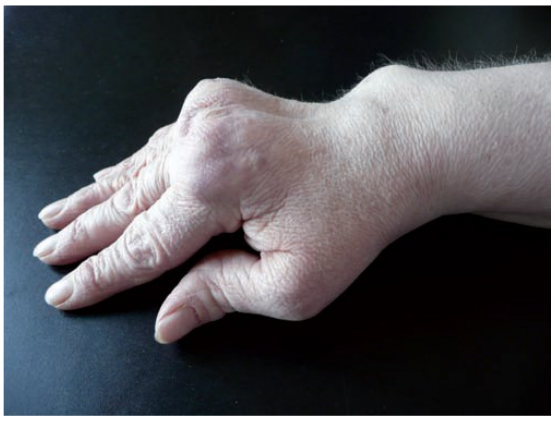

Figure 1.1 Typical hands deformities in RA patients: volar subluxation of the right hand with a visible sliding at the radiocarpal joint and Z-deformity with flexion of the first metacarpophalangeal joint and hyperextension of the interphalangeal joint. (Watts RA, et al. Oxford textbook of rheumatology. 2013)

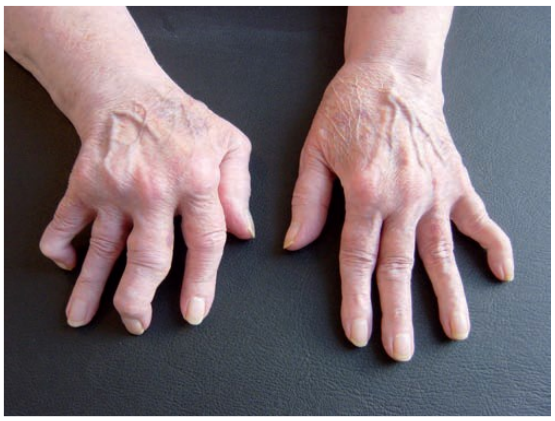

Figure 1.2 Typical hands deformities in RA patients: radial deviation (right wrist), swan-neck deformity with hyperextension of the proximal interphalangeal (PIP) and flexion of distal interphalangeal (DIP) joints (fingers 3 right and 5 on both sides) and boutonniere deformity with flexion of the PIP and hyperextension of DIP joints (fingers 2-4 left). (Watts RA, et al. Oxford textbook of rheumatology. 2013)

At the upper-limbs, involvement of the elbow is often accompanied by considerable synovitis with effusion in the olecranon fossa and bursitis, leading to a reduction of extension, flexion, and supination (Figure 1.4). [1]

Shoulder involvement often starts with bursitis and tenosynovitis of the bicep tendon. In patients with advanced disease, synovitis can cause erosions and destruction of the glenohumeral joint. Furthermore, rotator cuff tendon ruptures are frequently observed in patients with shoulder involvement. Taken together, all these manifestations can cause significant functional impairment in daily activities. [1]

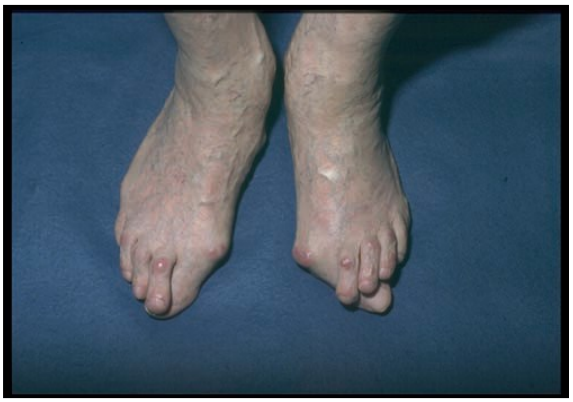

Figure 1.3 Typical forefoot deformities in RA patient: clawing of the toes and dislocation of the metatarsophalangeal (MTP) joints. (Watts RA, et al. Oxford textbook of rheumatology. 2013)

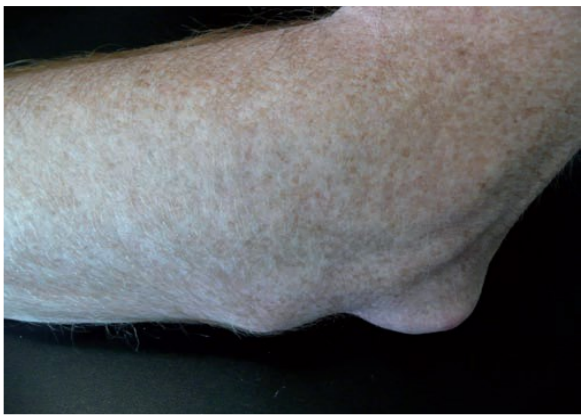

Figure 1.4 Typical elbow involvement in RA patient: effusion in the olecranon fossa and bursitis, plus a rheumatoid nodule distal to olecranon bursitis. (Watts RA, et al. Oxford textbook of rheumatology. 2013)

At the lower-limbs, knee involvement is very common and presents with synovitis, bursitis and erosive lesions. Popliteal bursitis (Baker's cyst) is associated with risk of popliteal vein compression and the rupture of this cyst can cause acute pain and inflammatory swelling of the soft tissue compartment of the thigh and thrombotic complications. At the knee joint, functional loss is associated with reduced extension and instability due to laxity in the ligaments. This may lead to the development of a progressive valgus deformity, particularly in women with a physiological accentuated valgus position. Additionally, involvement of the tibiotalar and subtalar joints can result in a progressive flattening of the longitudinal foot arch, further exacerbating the valgus deformity of the legs (Figure 1.3). Furthermore, involvement of the ankle joints can cause considerable functional deficits interfering with walking biomechanics. In long-standing and poorly controlled RA, prosthetic joint replacement is frequently required for knee and hip joints. [1]

Regarding the axial joints, the most critical involvement in RA affects the cervical spine. Particularly, inflammatory changes of the atlantoaxial joint (C1–C2) with destabilization and

atlantoaxial dislocation represents a potentially life-threatening complication. Instability in the atlantoaxial joint must be excluded, particularly before procedures leading to hyperflexion of the cervical spine such as during adapted physical activity, dental care, and intubation. In case of proven instability, wearing a stiff collar and surgical stabilization are appropriate measures. [1]

Extra-articular manifestations

Extra-articular disease manifestations underscore the systemic nature of RA and play a significant role in prognosis and treatment decisions. [25] Since involvement of internal organs is frequent, detailed organ examination and, if required, interdisciplinary management of complications is necessary. [1]

One of the most frequent extra-articular disease manifestations is the presence of subcutaneous rheumatoid nodules, especially in seropositive patients with severe and active disease. However, with increasingly effective use of conventional and biological DMARDs the occurrence of subcutaneous nodules has decreased and is now rare. These nodules predominantly manifest on the extensor surfaces of the upper limbs, particularly along the forearm and fingers (Figure 1.4), but they may occasionally occur in other periarticular areas, such as the Achilles tendon. In rarer cases, they can also involve internal organs, including the lung parenchyma and myocardium. [26]

Eye involvement includes the frequent occurrence of secondary Sjögen's syndrome as well as the rarer and mild complication of episcleritis and the potentially severe manifestation of scleritis and keratitis. [27]

Hematologic abnormalities are common in RA. Thrombocytosis, leukocytosis, elevated immunoglobulin levels, and increased ferritin are frequently observed. Iron and LDL cholesterol levels are often reduced in individuals with RA, which, along with elevated CRP and ESR levels, indicates the presence of chronic inflammation typical of the disease. Additionally, a decrease in erythrocyte and hemoglobin levels shows the presence of anemia. [1]

Vasculitis is now rare and associated with disease severity and activity in RA. The most common manifestation is cutaneous vasculitis of small to medium-sized vessels leading to necrosis and ulceration, primarily on the foot and thigh. Additionally, vasculitis may result in peripheral neuropathy either symmetrical or mononeuritis multiplex causing loss of

sensory and motor conduction. Organ-specific vasculitis can lead to infarction including myocardial infarction or stroke, and also may damage other internal organs. [1]

Lung involvement in RA is frequent and under-recognized. [25, 28] Pleuritis may occur at the onset of the disease and can lead to progressive respiratory distress due to pleural fluid accumulation. However, in some asymptomatic patients with minimal effusion, pleuritis is incidentally detected through routine imaging. Additionally, interstitial lung disease (ILD) of mild to moderate severity is relatively common. It is important to note that ILD is also a rare but significant adverse effect of methotrexate (MTX) therapy. [1]

In the context of serositis, pleuritis may be associated with exudative pericarditis. Pericarditis with acute chest pain, dyspnea, and pericardial effusion represents the most frequent heart manifestation in RA. Chronic constrictive pericarditis can lead to right-sided heart failure. Involvement of the myocardium and endocardium can also occur as well as conduction defects and coronary arteritis due to vasculitis. [1]

Secondary amyloidosis, resulting from chronic persistent inflammation, is a severe and potentially underdiagnosed condition in RA. Amyloid A deposition primarily impairs renal function, potentially leading to end-stage renal failure requiring dialysis. [1]

In conclusion, mortality and disability in RA are significantly impacted by comorbidities arising from these extra-articular manifestations. Thus, the management of comorbidities is crucial for guiding treatment decisions and determining individual prognosis. [1]

1.1.5 Management

The primary aim of RA treatment is to achieve remission. When remission is not possible, maintaining low disease activity becomes the goal, as this helps prevent disease progression and long-term disability. Multidisciplinary support for patients from the start, and throughout the course of the disease, is vital. [29, 30, 31] Patients should be fully informed about the nature of RA, the reasons for specific interventions, and the importance of their active participation in disease management. [29]

Access to physiotherapy and occupational therapy is also important from disease onset. The impact of RA on patients, particularly their social roles, can be devastating, as well as affecting carers. Although physical exercise is a cornerstone of non-pharmacological management and will be thoroughly addressed in the subsequent chapter, the following section will provide a concise overview of the pharmacological approaches currently used in RA management. [1]

For patients with early active RA methotrexate (MTX) should be included in the disease-modifying anti-rheumatic drugs (DMARD) regimen, because there is considerable scientific evidence behind its usage and many experience of MTX in combination regimens with other DMARDs and biological therapies. [29, 32] The dose is highly adjustable, with higher doses (20–30 mg once weekly) more efficacious than lower (7.5–15 mg). [32] Patients are more likely to stay on MTX longer, due to sustained efficacy, and good long-term tolerability. [33] It is available orally and subcutaneously. With intolerance of tablets, or limited efficacy, switching to subcutaneous injections improves bioavailability, increases efficacy, and decreases toxicity. [34] Plus MTX is the chepeast DMARDs and is also cheaper than the biologic drugs. However, not all new patients need to go onto MTX. In some cases, there may be an absolute contraindication. The evidence for using MTX either alone or in combination has largely been generated in trials on active RA. Evidence is lacking in patients with milder or palindromic RA, where other monotherapies may be just as appropriate. [30, 32]

Steroids are the best way of getting active RA under rapid control, with greater potency than non-steroidal anti-inflammatory drugs (NSAIDs), because they act on numerous inflammatory pathways and not just on antagonizing cyclooxygenase. [35] Moreover, a meta-analysis has shown that they are also disease modifying, unlike NSAIDs. [36]

The introduction of biologics to RA and other inflammatory arthropathies has had a huge impact on improving the control of poor-prognosis and refractory disease. Anti-TNF therapies currently take precedence as they were the first RA biologics, and unlike some other similar drugs, are licensed for patients who fail on DMARDs. [1]

1.2 – Ankylosing Spondylitis

1.2.1 Definition and epidemiology

The term spondyloarthropathies (SpA) compromise different diseases such as Ankylosing Spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, arthritis/spondylitis associated with inflammatory bowel disease (IBD), and undifferentiated SpA. These diseases have in common that patients present with a similar clinical picture, either predominantly axial or predominantly peripheral or as an overlap between these two patterns, and with a varying association with HLA-B27. [37]

Axial SpA is a disease which starts normally in the third decade of life, rarely at an age

older than 45 years, but in 10‑20% of patients even between the ages of 10 and 20 years. [38] Thus, mostly young people are affected early in the course of the disease. Interestingly, HLA-B27-positive patients have the first symptoms about 10 years earlier compare to HLA-B27-negative patients. [39]

The male/female ratio is estimated to be 2:1 and the prevalence it is directly correlated with the prevalence of HLA-B27 [40, 41] in a given population and has been estimated to be between 0.1% and 1.4% in different parts of the world. 9 Recent investigations from France, the United States, and Lithuania [42, 43, 44] showed that the overall prevalence of SpA (including axial and peripheral SpA) is similar to that for RA.

1.2.2 Classification criteria and diagnosis

For classification and partly also for diagnosis of AS, the 1984 modified New York criteria for AS have been used in the past. [45] The presence of radiographic sacroiliitis (at least either grade 2 bilaterally or grade 3 unilaterally) is essential for the fulfilment of these criteria (Figure 1.5), plus one clinical criterion: either morning stiffness with improvement by exercise but not by rest or restriction of spinal mobility. (Fig 1.6)

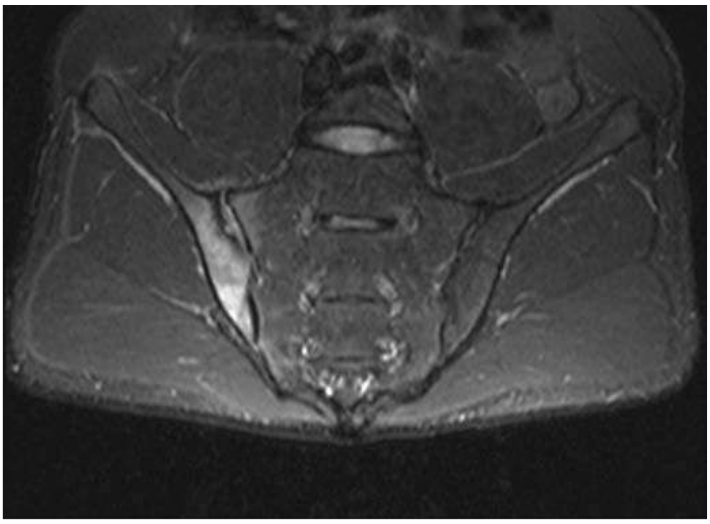

Figure 1.5 MRI of SIJ: active sacroiliitis shown by the hyperintense signal in the ileum and in the upper part of the sacrum of the right SIJ (Watts RA, et al. Oxford textbook of rheumatology. 2013)

However, both radiographic sacroiliitis and restriction of spinal mobility occur relatively late in the course of the disease. Therefore, these criteria are not suitable for classification/diagnosis of early cases, which is very important for the prevention of joint damage. Instead, the new criteria for axial SpA, published in 2009 by the Assessment in Spondylo-Arthritis international Society (ASAS), cover patients with and without radiographic changes in the sacroiliac joints (SIJ) to allow an earlier diagnosis. [46] These criteria should be applied in the presence of chronic back pain (> 3 months) starting at an age younger than 45 years. Sacroiliitis on imaging remains important, not only if it is visible

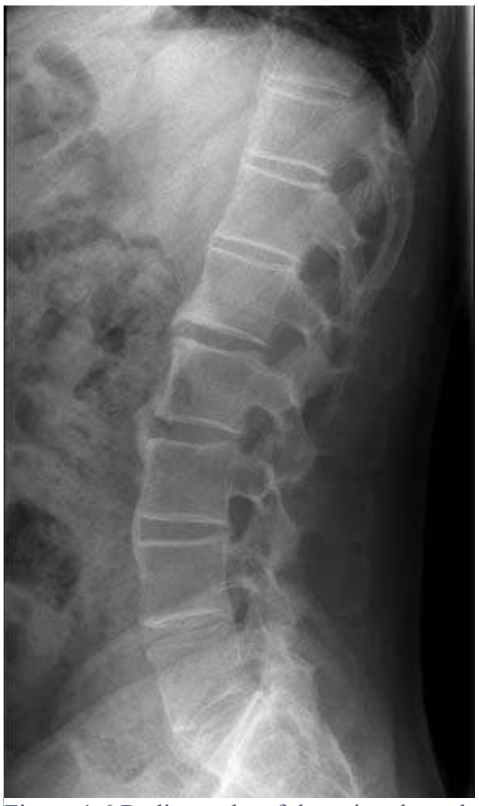

Figure 1.6 Radiographs of the spine: lateral radiograph view of the lumbar and lower thoracic spine with widespread syndesmophyte formation in a patient with AS. (Watts RA, et al. Oxford textbook of rheumatology. 2013)

on radiographs but also when subchondral bone marrow oedema it has evidence of active bony inflammation which can be seen on MRI. [47]

Although the imaging arm has good specificity (97.3%) the sensitivity is not optimal (only 66.2%). Therefore, a clinical arm was added which is fulfilled if a positive HLA-B27 is present plus two other SpA-typical features, always in the presence of chronic back pain starting at an age less than 45 years. With both arms these new criteria reach a specificity of 84.4% and a sensitivity of 82.9%. [1]

As mentioned in the previous section, compare to classification criteria which always give just a yes/no answer, the diagnostic approach has to be more flexible, resulting in certain probabilities that a diagnosis can be made, dependent on the number and nature of the parameters being positive. Furthermore, for diagnosis negative findings should also be considered, which is not the case for classification criteria. [1]

Two overlapping possible diagnostic approaches have been proposed. For the first one, presence or absence of all for axial SpA-relevant parameters are looked for and weighted according to the odds ratio (calculated from the sensitivity and specificity of these parameters) and the post-test probability can be estimated based on an assumed pre-test probability of 5% for axial SpA among patients presenting with chronic back pain. [48]

Another, more structured diagnostic approach begins with the evaluation of clinical parameters, followed by radiographs of the SIJ. Next, laboratory tests, including HLA-B27 and CRP, are assessed, and finally, MRI is performed. [49]

Both for classification and diagnosis MRI has become an important new tool for axial SpA, especially for active inflammatory lesions. Normally the spine is affected later in the course of the disease, thus classification criteria focus on the SIJ. In the spine, as in the SIJ, the

disease starts with inflammation, such as spondylitis anterior, spondylitis posterior, spondylodiscitis or involvement of the facet joints. [50]

An elevated CRP or ESR is found in only about 60% of AS patients who are clinically active and CRP-positive patients seem to have a worse prognosis regarding radiographic progression. [51]

Recently others referral parameters have been proposed and have been tested in primary care in patients presenting with chronic back pain. If symptoms start at an age lower than 45 years and if the patient complains about inflammatory back pain and/or if the patient has been tested positive for HLA-B27, a diagnosis of axial SpA was made in 25‑60% of these patients after referral to a rheumatologist. [52, 53, 54]

1.2.3 Clinical features

Spinal Symptoms

The symptoms are dominated by pain and stiffness in the spine, especially in the lower back, reflecting inflammation in the SIJ and/or lumbar spine. In the course of the disease the thoracic and cervical spine can also be affected. [55] This pain is called “inflammatory back pain” (IBP) which is characterized by morning stiffness (normally >30 minutes), which improves with exercise but not with rest and/or by awakening in the second half of the night due to the sorrow. This kind of pain starts normally at an age less than 45 years. [1]

Disease activity is normally measured by using the Bath Ankylosing Spondylitis Activity Index (BASDAI) which is a composite index from 0 (= no symptoms) to 10 (= maximal symptoms) on a numeric scale. [56] The BASDAI is a patient-based questionnaire including questions about fatigue, pain in the spine, pain at peripheral joints and entheses, and morning stiffness. Function is measured, again by using a patient-based questionnaire, called Bath Ankylosing Spondylitis Functional Index (BASFI) on a similar numeric rating scale between 0 and 10. [57] Recently, ASAS has developed and proposed a new Ankylosing Spondylitis Disease Activity Score (ASDAS) which includes the CRP value as well as outcome measures reported by patients. [58, 59]

Restriction of spinal mobility and function is caused early in the course of the disease by inflammation in the axial skeleton, but later on by new bone formation in the spine. [60] Most typically, syndesmophytes develop from the corner of the vertebral bodies and potentially can cause an ankylosis of the spine. However, ossification of the facet joints can

also contribute to restriction of spinal mobility. Nevertheless, it must be emphasized that only a small proportion of patients with axial SpA develop an advanced ankylosis. [1]

Spinal mobility should be measured using the established Bath Metrology Ankylosing Spondylitis Index (BASMI), based on a score between 0 to 10, which quantifies forward motion of the lumbar spine, lateral flexion of the lumbar spine, tragus to wall or occiput to wall distance, cervical rotation and intermalleolar distance. In addition, chest expansion, determined by the difference between inspiration and expiration, can be measured in the fourth intercostal level anteriorly. [50]

Long-term outcome is closely related to formation of syndesmophytes in the spine, potentially resulting in ankylosis. The strongest predictor for syndesmophyte progression on follow-up is the presence of syndesmophytes at baseline. [61, 62]

Extraspinal rheumatic manifestations

Peripheral arthritis is reported by about 30% patients with axial SpA. Typically, the arthritis is transient, asymmetrical and affects predominantly the lower-limbs. Mono- or oligoarthritis is most frequent, but occurrence of polyarthritis is also possible. However, structural bone damage such as erosions or ankylosis is rare in peripheral joints. [55, 63]

Another extraspinal rheumatic manifestation is the inflammation at the insertion sites of tendons or ligaments at bone called enthesitis and is a typical manifestation in any SpA. Enthesitis, in fact, is reported in 30‑50% of patients with axial SpA/AS. Similarly to arthritis, it occurs predominantly at the lower-limbs, such as the insertion site of the Achilles tendon or the plantar fascia at the calcaneus or in the pelvis, but it can also occur in the upper-limbs, such as the elbows or at the insertion of the supraspinatus tendon at the greater tuberosity of the humerus. [64, 63] Enthesitis is normally quite painful and can be accompanied by a considerable restriction of function, especially if occurring in a lower-limb. Swelling is typically observed only when the adjacent soft tissues, such as the bursae, are also affected. [1]

Extra-articular manifestations

Current or history of uveitis anterior can be found in 30‑40% of AS patients. Flares of uveitis are reported in 15‑20% of AS patients per year. Uveitis is typically anterior, sudden in onset (painful red eye), acute, self-limiting, and unilateral but alternating from one eye to the other. [65]

A concomitant diagnosis of psoriasis is found in about 10% of IBD and in about 5% of AS patients. Psoriasis and IBD most often, but not always, precedes the diagnosis of AS.
Other organs can be involved such as kidney, lung, or heart, but these are rare manifestations. [55] Whether these manifestations are related to the level of clinical disease activity and inflammation is still unknown, however it seems to be probable.
Amyloidosis can occur in patients who are highly active over a long time. [1]

1.2.4 Management

While the therapeutic benefits of physical exercise will be addressed in the subsequent chapter, this section focuses on the pharmacological management of AS.
The cornerstone of pharmacological treatment for AS is the use of non-steroidal anti-inflammatory drugs (NSAIDs). Their efficacy has been proven in many trials and is most probably due to their anti-inflammatory properties. [66, 67]
Glucocorticoids do not play a major role in the treatment of axial SpA. This treatment might be tried for peripheral arthritis, while its effect in enthesitis is less clear. Short-term effects of high-dose glucocorticoid pulse therapy has been reported but its long-term effect is not clear and has not been studied in a controlled trial. Local glucocorticoid injection in the SIJ, peripheral joints, or entheses can be effective and should be considered especially when just one site is affected. [68]
Another fundamental aspect of pharmacological treatment for AS is the biological TNF blocker, which has proven to be effective in patients with active AS, particularly those who do not respond to conventional therapies such as NSAIDs. [1]

1.3 – Psoriatic Arthritis

1.3.1 Definition and epidemiology

For many years, the association between arthritis and psoriasis has been recognized, but there was controversy about whether it represented a separate disease entity, or simply the co-existence of RA and psoriasis. Finally, in 1964, Psoriatic arthritis (PsA) was officially recognized as a distinct disease by the American Rheumatism Association (now known as the American College of Rheumatology), and is now classified as a member of the spondyloarthropathy spectrum. [69, 70] PsA was initially defined as “an inflammatory arthritis in the presence of psoriasis with a usual absence of rheumatoid factor”, [71] but a more specific classification criteria have now been developed. [72]

Although research in this area is relatively limited, multiple studies suggest that the prevalence of arthritis in patients with psoriasis, particularly those with peripheral inflammatory arthritis, is higher compared to the general population. [73] In the Norfolk Arthritis Register (NOAR) cohort, the prevalence of psoriasis among patients with new-onset arthritis was found to be 9.5%, higher than that observed in population controls. [74]
Several studies have been attempted to estimate the incidence and prevalence of PsA but results were very various. A systematic review of papers revealed a median incidence rate of 6 per 100000 population (range 0.1–23) and a median prevalence of 180 per 100000 population (range 1–420). [75] However, there is an increase in the incidence and prevalence of PsA, [75, 76] possibly as a result of increased recognition.
Indeed, recent researches have been conducted in order to realize the development of screening tools to identify PsA among populations of psoriasis patients. [77] These instruments are self-completed questionnaires which provide cut-offs for detecting PsA and they are used to identify patients who should be referred to rheumatologists. The use of such tools should increase the identification of PsA as it is known that cases of PsA exist undiagnosed in dermatology clinics. [78]

1.3.2 Classification

In contrast to AS, which is considered as the "prototype" SpA with typical features such as sacroiliitis, a high prevalence of HLA B27, and only minimal clinical variation, PsA shows significant clinical heterogeneity. These variabilities provide additional challenges for its classification. [1]
New classification criteria are either "standalone" such as the CASPAR criteria or the inclusive axial and peripheral spondyloarthropathy criteria which subsume PsA. The CASPAR criteria (Figure 1.7) include characteristic dermatological, clinical and radiological features and have both high sensitivity and very high specificity. [72]
Although the wide acceptance of the CASPAR several areas require further elucidation. First, there have been doubts on the suitability of the criteria for early disease, [79] but a recent study found good sensitivity/specificity for these criteria in people presenting with less than 2 years of disease. [80] Secondly, the criteria have inevitably been used as diagnostic criteria, and although they were not originally designed for this purpose, there is evidence suggesting they perform effectively in this context. [81] Thirdly, the criteria are

only applicable to people with inflammatory musculoskeletal disease, but defining what is meant by this requires further work. [1]

Inflammatory articular disease (joint, spine, or entheseal), with three or more points from the following:		
1. Evidence of psoriasis (one of a, b, c)	(a) Current psoriasis[a]	Psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist
	(b) Personal history of psoriasis	A history of psoriasis that may be obtained from patient, family doctor, dermatologist, rheumatologist, or other qualified healthcare provider
	(c) Family history of psoriasis	A history of psoriasis in a first- or second-degree relative according to patient report
2. Psoriatic nail dystrophy		Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination
3. A negative test for rheumatoid factor		By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range
4. Dactylitis (one of a, b)	(a) Current	Swelling of an entire digit
	(b) History	A history of dactylitis recorded by a rheumatologist
5. Radiological evidence of juxta-articular new bone formation		Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of hand or foot

Figure 1.7 The CASPAR criteria (Watts RA, et al. Oxford textbook of rheumatology. 2013)

1.3.3 Clinical spectrum

PsA is a heterogenous disease and there have been a number of attempts to subgroup patients according to their clinical presentation. Moll and Wright described the five classic subgroups: monoarthritis/oligoarthritis, distal interphalangeal (DIP)-predominant disease, RA-like polyarticular disease, pure axial involvement, and arthritis mutilans. [71] However, more recent literature has demonstrated that this classification into groups is not robust and can evolve over time, particularly in response to treatment. [82]

A simpler classification of patients into axial and peripheral forms, with the latter further subdivided into oligoarthritis and polyarthritis, offers the advantage of clarity and may serve as a more practical framework. There is evidence to suggest that polyarticular onset is associated with a worse prognosis. [83]

Certain clinical features are indicative of PsA. Common presentations are oligoarticular disease, with perhaps just one or two very swollen joints, nail disease, and enthesitis. The presence of dactylitis (Figure 1.8) is very frequent, although other causes of dactylitis (such as gout, sarcoid, and tuberculosis) should be considered in the differential diagnosis. [84] DIP involvement closely resembles the one observed in OA. Indeed, in this joint can look identical. However, sometimes the age of the patient and the lack of family history of OA indicate the significance of involvement at this joint. [1]

Symmetrical polyarthritis is probably the most frequent subtype of PsA and overlap with RA can lead to misidentification and problems with nosology. It is of paramount importance to take a good family history and to inspect both nails and "hidden" areas for psoriasis like the natal cleft. [85]

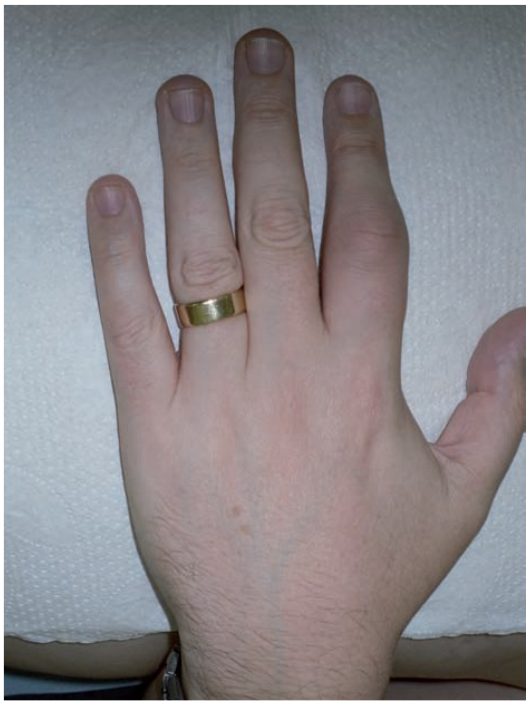

Figure 1.8 Dactylitis: one of the most common manifestations in PsA. (Watts RA, et al. Oxford textbook of rheumatology. 2013)

The foot is commonly involved in PsA and in some cases, the initial presentation of the disease may occur during a consultation with a podiatrist. PsA, in this anatomical region, may present with dactylitis (more common than in the hands), enthesitis (at the calcaneum but also at the insertion of tibialis posterior and peroneus brevis), arthritis (in metatarsophalangeal and midtarsal joints), and skin and nail changes, although the latter are easily confused with fungal infection. Foot problems are often overlooked in rheumatology and may result in unnecessary disability and pain. [86]

Although axial involvement is common in PsA, there are significant differences between its presentation and that of AS. Indeed, significant differences in radiological phenotypes have been documented, encompassing both quantitative (less of sacroiliitis and new bone formation) and qualitative parameters (paravertebral ossification and morphologically different syndesmophytes in PsA). [1]

1.3.4 Pathogenesis

It seems that PsA results from an interplay between genetic susceptibility and environmental triggers. Of the latter, the two most recorded are infection and trauma. The relationship between guttate psoriasis, streptococcal infection, and PsA was discussed in the early 1980s, [87] and more recently infections in general have been associated with the onset of PsA in people with psoriasis. [88] Studies have suggested that acute physical trauma may be associated with the onset of PsA, [89] a phenomenon also commonly observed in the development of other rheumatic conditions such as OA and RA. [90]

PsA is known to be a highly heritable disease: the recurrence risk (ΛS; risk to siblings/risk in general population) of PsA is estimated at 27, [91] which is higher than for psoriasis (ΛS between 4 and 11).

Thirty per cent of the genetic susceptibility to psoriasis is found in the major histocompatibility complex (MHC) class I region on chromosome 6p21.3 (psoriasis susceptibility 1, PSORS1) where HLA-Cw*0602 is the susceptibility allele. [92]

While HLA-B27 is commonly associated with AS, it can also be found in PsA cases, although its prevalence is significantly lower. [93] Additionally, HLA-B38 and HLA-B39 have been linked to peripheral PsA, and the shared epitope (HLA-DRB1) has been associated with erosive polyarticular disease. [94]

Genome-wide association (GWAS) have further identified key genetic links, including alleles of the IL-12B and IL-23R receptor genes, which are involved in both psoriasis [92] and PsA. [95]

1.3.5 Management

PsA is a complex and heterogeneous disease, making comprehensive management essential for optimal treatment outcomes. The more complex patients with PsA will require treatment input from both a rheumatologist and a dermatologist to allow optimal management of their condition. Good communication between these specialists, as well as with primary care providers, is important for managing treatment. [1]

The most commonly used treatment regimen for PsA is a step-up model, where therapy is gradually escalated in cases of non-response. In 2006, the GRAPPA group (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) published treatment guidelines based on a comprehensive literature review and expert consensus. [96] These guidelines outline the effective treatments for the five key domains of PsA. More recently the European League Against Rheumatism (EULAR) has published evidence-based recommendations with a detailed algorithm independent of clinical subgroup. [97]

The pharmacological treatment of PsA involves various drugs, some with robust scientific evidence and others with less support, leading to less frequent use.

NSAIDs have been recommended for many years, particularly in mild cases where they are often suggested as monotherapy. [98] However, there is a lack of randomized clinical trials to strongly support their use. Similarly, data supporting the use of intra-articular (IA) steroids in PsA is limited. Expert consensus suggests that IA glucocorticoid injections may be

beneficial in cases of persistent mono- or oligoarthritis, often yielding positive clinical outcomes. [99]

Standard DMARDs are routinely used in PsA despite a paucity of evidence for their use in this condition. Interest in MTX for the treatment of PsA evolved following its use in RA for arthritis and studies showing efficacy in psoriasis. [100, 101]

Sulfasalazine, along with leflunomide and ciclosporin, has solid evidence supporting its use and is effective in addressing both skin and joint symptoms in PsA. The combination of MTX with these drugs has shown promising results in managing the disease. [102]

A crucial aspect of PsA treatment is the use of biological agents, which are well-supported by extensive literature. In the United Kingdom, National Institute of Clinical Excellence (NICE) guidance on the use of TNF inhibitors in PsA advises that the patient must have active disease (three swollen and tender joints) and have failed two or more conventional DMARDs (http://guidance.nice.org.uk/TA199). The most effective TNF blockers include Etanercept, Adalimumab, Golimumab and Infliximab. [1]

Surgery may be required for “end-stage” large joints such as the hip and knee. Unless routine antibiotic cover is used there is evidence to suggest a higher rate of superficial and deep infection in PsA. [103]

As with AR and AS, physical exercise plays a crucial role in managing PsA. It helps alleviate pain, reduce comorbidities, enhance strength and aerobic capacity, and improve overall quality of life, while also positively impacting disease progression. However, this topic, again, will be explored in the next chapter.

2. ADAPTED PHYSICAL EXERCISE IN RHEUMATIC DISEASES

2.1 - Physical exercise and inflammation

One of the key challenges in managing rheumatic diseases is the systemic chronic inflammation. This condition is a hallmark of many diseases, but fortunately numerous studies have shown that regular physical exercise can play a significant role in reducing chronic inflammation.

Inflammation is an adaptive response that is triggered by noxious stimuli and conditions, such as infection and tissue injury. [104] Considerable progress has been made in understanding the cellular and molecular events that are involved in the acute inflammatory response to infection and, to a lesser extent, to tissue injury. In addition, the events that lead to the localized chronic inflammation, particularly in chronic infections and autoimmune diseases, are partly understood. However, much less is known about the causes and mechanisms of systemic chronic inflammation. [105]

Inflammatory responses are primarily orchestrated by immune cells, blood vessels, and molecular mediators, including cytokines, chemokines, and acute-phase proteins. Among the key components are elevated levels of CRP and increased systemic concentrations of critical cytokines such as TNF-α, IL-1β, and IL-6. [106]

2.1.1 The anti-inflammatory effect of exercise

Recent reviews on the anti-inflammatory effects of exercise [107, 108] have identified three possible mechanisms: the reduction in visceral fat mass, an increased production of anti-inflammatory cytokines from contracting skeletal muscle (Figure 2.1), and a decrease in Toll-like receptor (TLR) expression on monocytes and macrophages, which inhibits downstream pro-inflammatory responses such as cytokine production and the expression of MHC and co-stimulatory molecules. [109]

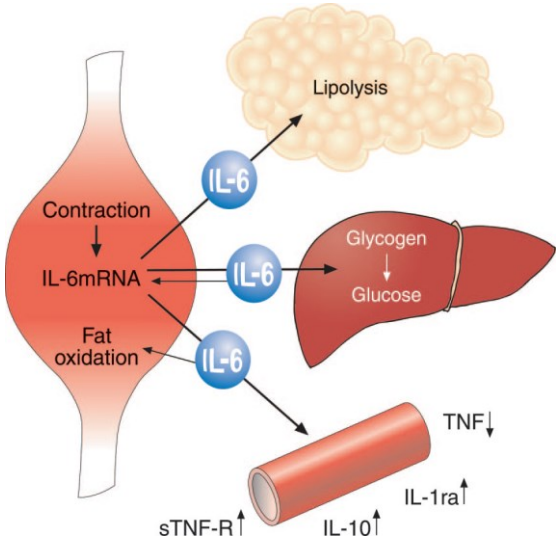

Figure 2.1 Cytokines production from contracting skeletal muscle. (Petersen AM, Pedersen, BK. 2005).

In addition, mouse studies highlighted that the anti-inflammatory effects of exercise also rely on other mechanisms, such as the inhibition of monocyte and macrophage infiltration into adipose tissue and the phenotypic switching of macrophages within adipose tissue. [110] Although these processes are challenging to study in humans, analysis of peripheral blood following exercise have shown a reduction in the circulating numbers of pro-inflammatory monocytes [111] and an increase in the circulating numbers of regulatory T cells (TReg cells). [112, 113] This suggests that such mechanisms may contribute to the anti-inflammatory effects of exercise in humans.

2.1.2 Cytokine responses to sepsis and exercise

Most studies on cytokines come from sepsis research. In both clinical and experimental models of sepsis, the cytokine cascade typically follows this sequence: TNF-α, IL-1β, IL-6, IL-1ra, sTNF-R, and IL-10. [114] The first two cytokines in the cascade are TNF-α, IL-1β, which are produced locally and they are typically referred as proinflammatory cytokines. [115] TNF-α and IL-1β stimulate the production of IL-6, which has been classified as both a pro- and an anti-inflammatory cytokine. [116] However, the cytokine response to exercise differs from that elicited by severe infections. [117, 118, 119, 110] Notably, the classic pro-inflammatory cytokines (TNF-α and IL-1β) generally do not increase in response to exercise, highlighting the difference between the cytokine cascades induced by exercise and those elicited by infections. Typically, IL-6 is the first cytokine that appears in the circulation during exercise and its levels can increase exponentially, followed by a decline post-exercise. [117, 118, 119, 120] Another finding in relation to exercise is increased circulating levels of anti-inflammatory cytokines and cytokine inhibitors such as IL-1ra and sTNF-R. [121, 122] In summary, exercise predominantly induces an increase in IL-6, followed by IL-1ra and IL-10. The appearance of IL-6 in the circulation is by far the most marked and its appearance precedes that of the other cytokines (Figure 2.2).

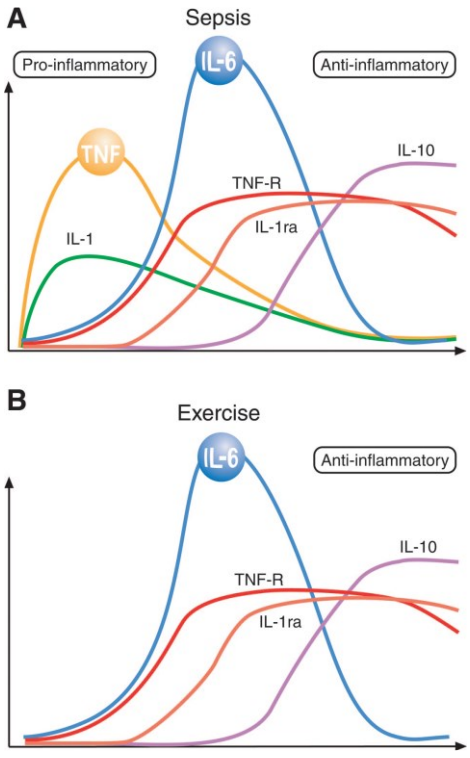

Figure 2.2 Cytokines released during an infection and during physical exercise. (Petersen AM, Pedersen, BK. 2005).

2.1.3 IL-6 response to exercise

The IL-6 response to exercise has recently been reviewed [117, 118, 119, 120] and a consistent finding across numerous studies is the marked increase in circulating IL-6 levels after exercise, even in the absence of muscle damage. Plasma IL-6 levels rise exponentially during exercise, and this increase is related to factors such as intensity, duration, the amount of muscle recruited, and an the endurance capacity of the individual. [117, 118, 120, 123] Recent researches have demonstrated that IL-6 mRNA is upregulated in contracting skeletal muscle [107] and that the transcriptional rate of the IL-6 gene is markedly enhanced by exercise. [124] Additionally, IL-6 protein is expressed in contracting muscle fibers [125, 126] and released into circulation during exercise [127], whereas this process is not observed with TNF-α. [127, 128] Interestingly, even moderate exercise triggers a significant release of muscle-derived IL-6 in both young and elderly healthy subjects, with the effects being even more pronounced in the latter group. [129]

2.1.4 Anti-inflammatory effects of IL-6, IL-10, IL-1RA and CRP

IL-6 has been shown to inhibit the production of pro-inflammatory cytokines such as TNF-α and IL-1. [130] Studies suggest that IL-6 plays a regulatory role in suppressing TNF-α levels, as it evidenced the elevated TNF-α levels in IL-6-deficient mice. [131, 132] IL-6 also stimulates the production of anti-inflammatory molecules like IL-1ra and IL-10, and their appearance in the circulation after exercise also contributes to mediating the anti-inflammatory effects of exercise. [133]

Indeed, IL-10 acts as an anti-inflammatory cytokine inhibiting the production of pro-inflammatory cytokines such as IL-1, TNF-α, and chemokines like IL-8 and macrophage inflammatory protein-1 (MIP-1). [134, 135] These molecules are crucial in activating immune cells and recruiting them to inflammation sites. Besides, IL-10 suppresses cytokine synthesis both at the transcriptional level and by promoting mRNA degradation of these pro-inflammatory cytokines. [136, 137]

Whereas IL-10 influences multiple cytokines, the biological role of IL-1ra is quite different. Although IL-1ra binds to IL-1 receptors, it does not initiate a cellular response. Instead, it inhibits the signal transduction through the IL-1 receptor complex, effectively blocking the downstream signaling pathways triggered by IL-1. [138]

A small increase of CRP levels is seen the day after exercise of longer duration. [118] CRP has a role both in the induction of anti-inflammatory cytokines in circulating monocytes and

in the suppression of the synthesis of proinflammatory cytokines in tissue macrophages. [139]

2.2 - The benefits of physical exercise in Rheumatoid Arthritis

A systematic review conducted by the Documentation Department of the Spanish Rheumatology Society (SER), titled "Role of Physical Activity in the Management and Assessment of Rheumatoid Arthritis Patients" (Hernández-Hernández MV, et al.), identified and analyzed all relevant literature on the relationship between RA and physical exercise. The review aimed to identify all published literature, from January 2000 to January 2015, related to physical activity (PA) and/or energy expenditure in individuals with RA. To be included in the review, studies had to be observational or interventional, measuring free-living PA or total/activity-related energy expenditure using either subjective or objective methods. Eligible studies involved adult populations with RA, with all participants meeting the 1987 criteria established by the American College of Rheumatology (ACR). Studies were excluded if they were interventional but focused on new pharmacological treatments, not published in English, or available only in abstract form. [140]

In the following points, the results obtained in the review will be discussed and summarized.

2.2.1 Physical exercise in RA patients

Regular moderate to high-intensity exercise has been shown to improve muscle strength and cardiovascular fitness, not only in healthy populations but also in individuals with chronic illnesses, including RA. [141, 142, 143, 144] If left uncontrolled, RA leads to joint deformities and destruction due to cartilage and bone erosion. Consequently, it has been assumed that RA patients are less active than the general population, largely due to these joint complications. Additionally, traditional recommendations from physicians often advised against exercise, fearing that PA could exacerbate joint inflammation, [145] pain, [146] or accelerate joint damage in RA patients.

However, current evidence indicates that exercise has no harmful effects on disease activity or joint damage [143, 147] and instead improves muscle strength [148] in RA patients. Moreover, recent studies suggest that individuals with RA who were physically

active before the onset of the disease tend to experience milder symptoms in terms of inflammation, pain, and overall function. [149]

Furthermore, patients with RA are more prone to develop cardiovascular diseases due to a proatherogenic profile driven by systemic inflammation. [150] Although studies examining the relationships between PA, body mass index (BMI), fat mass, and lipid levels in RA populations have produced controversial results, [141, 151, 152] the evidence strongly suggests that PA decreases the cardiovascular risk (CVR) in RA patients. [153, 141, 154]

2.2.2 Effect of physical exercise on joints and disease activity in RA patients

In addition to the general health benefits, regular PA in RA patients can provide disease-specific advantages, such as reduced pain, improved muscle function, and delayed onset of disability, [148, 155, 156, 157, 158] without causing harm to the joints. [143, 148]

Interestingly, moderate-intensity PA has anti-inflammatory effects in both healthy individuals and those with chronic illnesses. [159] Indeed, in RA patients, regular PA has been linked to reductions in CRP [141, 155] and ESR [160] levels.

Several clinical trials have been conducted to evaluate the effects of PA in patients with RA. Both short-term and long-term clinical trials have assessed the effects of aerobic and resistance exercises on various outcome measures in RA patients. [141, 143, 144, 148, 160, 161, 162]

2.2.3 Aerobic exercise in RA patients

A systematic review and meta-analysis of aerobic exercise, [155] which analyzed 14 randomized controlled trials, has found that cardiorespiratory aerobic conditioning in stable RA it appears to be safe and leads to improvements in quality of life, functionality, and pain levels. However, it did not show significant changes in DAS28 scores or joint counts. The meta-analysis also suggests that initiating exercise programs early yields better outcomes in terms of quality of life and functionality. More recent clinical trials have similarly reported improvements in both functionality [161] and pain management [161, 162] in RA patients participating in aerobic exercise protocols.

Both program and disease duration influenced pain outcomes, with better results seen in established RA and short-term exercise protocols. However, data on quality of life indicated that exercise was more beneficial for patients with early RA than for those with established RA.

When patients were followed up for a long period of time, [143] it was found that no significant decrease in aerobic fitness occurred after a relatively brief period of detraining. However, long-term exercise produced sustained improvements in functional ability. This suggests that maintaining a structured PA program post-intervention is crucial for long-term benefits. [162, 163]

Among the studies reviewed that focused on aerobic exercise in RA patients, three assessed changes in disease activity using composite disease activity measurements. [143, 148, 162] These studies found that aerobic exercise positively impacted disease activity by reducing DAS28, although the reduction did not reach statistical significance.

2.2.4 Resistance exercise in RA population

The value of resistance exercise for RA patients remains debated, as its effects on cardiovascular risk are unclear. [141, 164] However, despite differences in study design, previous research suggests that high-intensity strength training is both feasible and safe for many RA patients.

A systematic review by Baillet et al. [165] have shown that resistance exercise programs in RA patients can result in modest but significant improvements in functional capacity, reductions in the number of tender and swollen joints, and a decrease in ESR. However, resistance exercise did not affect DAS28 scores or structural damage in any of the studies analyzed. The HAQ response has been more variable across reports, [141, 160, 166] possibly because it was designed for monitoring patients in pharmacologic trials and may not be suitable for evaluating physical interventions in patients with mild disabilities. While several studies [167, 168] have reported short-term benefits of strength training in RA patients, the duration of these positive effects after cessation remains uncertain. [148, 166, 169]

2.2.5 Practical applications and exercise recommendations

Over the past 20 years, several interventional clinical trials have been conducted to develop recommendations for aerobic and resistance exercises in RA patients. However, the significant variability in the type, intensity, and duration of PA across the trials, along with limitations in their quality and sample size, suggest that the conclusions of these studies remain tentative. Although further research is needed to better understand the

role of PA in RA management, a number of practical recommendations regarding exercise for RA patients are proposed in this review. [140]

All RA patients can benefit from a balanced program that includes both strengthening and aerobic exercises. Current evidence suggests that regularly engaging in moderate to high-intensity PA (aerobic and resistance exercises 2-3 times per week for 30-60 minutes) offers several benefits for RA patients. These include improved quality of life, enhanced functionality, reduced pain, fewer swollen joints, and lower levels of radiologic damage. [141, 144, 147]

Low-impact exercises such as walking, swimming, and biking are recommended forms of aerobic exercise for arthritis patients. These activities have been shown to improve cardiovascular fitness and quality of life, while reducing RA-associated disability and pain. [155, 162, 170, 171] As a result of a limited number of studies, it has been suggested that aerobic exercise should be performed at moderate to high intensity (60-85% of HRmax), 3 times per week, with sessions lasting 30-60 minutes, potentially divided into 3-4 periods of 15-20 minutes each. A progressive adjustment of intensity is also recommended for optimal results. [172]

Strengthening exercises are designed to enhance joint stability. Movements should be performed smoothly and should not cause joint pain. The target load for strengthening exercises should be moderate to high (50-80% of MVC). [172] These exercises should be performed for 20-30 minutes, 2-3 times per week. They can include static or dynamic movements, using body weight or various equipment such as resistance machines, pulleys, dumbbells, or elastic bands. A progressive and gradual increase in volume and intensity is recommended, either in a supervised clinical setting or at home with professional guidance and as long as it does not lead to discomfort or pain. [140]

Maintaining adherence to long-term exercise programs can be challenging. To address this, physicians should collaborate with other healthcare professionals to provide ongoing support and motivation, helping patients manage their condition in a positive way. It is important for healthcare providers to convey to RA patients that increasing PA is one of the best choices they can make for their overall health and joint care. [140]

Although there is a lack of studies specifically evaluating the role of PA during RA flare-ups, the most common recommendation from physicians is to reduce the duration and

intensity of exercise during these periods, particularly avoiding resistance exercises when disease activity is high. [140]

2.3 - The benefits of physical exercise in Ankylosing Spondylitis

Compared to RA and PsA, PA is even more valuable in managing AS. This is supported by the ACR and the European League Against Rheumatism (EULAR), who have released guidelines emphasizing the role of physical exercise in reducing disease activity and functional impairment in AS. [173]

The meta-analysis by Pécourneau et al., titled "Effectiveness of Exercise Programs in Ankylosing Spondylitis: A Meta-Analysis of Randomized Controlled Trials," aimed to analyze the existing literature to assess the implementation and effectiveness of recommended exercise guidelines. [174]

The meta-analysis included studies employing various exercise modalities: specific types of exercise (swimming, walking, aerobic training), home-based exercise programs, and supervised exercise led by healthcare professionals.

Studies conducted on patient on biologic therapy (anti-TNF-α) were not intended for inclusion in the meta-analysis. Participants could only receive NSAIDs, prednisolone, or analgesics.

The 2 primary end points checked in each study were the differences of BASDAI and BASFI between 2 time points in each group (exercise vs control), expressed in standardized mean difference between groups with the SE and 95% confidence interval (CI).

Additionally, a separate analysis was performed stratified on anti-TNF-α use to assess the effect of the exercise program in patients under biologic therapy.

2.3.1 Effect of the exercise programs on BASDAI and BASFI

Six trials [175, 176, 177, 178, 179, 180] showed a positive effect of exercise on the BASDAI (Figure 2.3). The overall WMD was -0.90 (95% CI, -1.52 to -0.27) for BASDAI, with a heterogeneity index (I2) of 69% (PZ.005) in favor of exercise, even after applying a random effect model. All trials showed a positive effect of exercise on the BASFI (Figure 2.4). The overall WMD was -0.72 (95% CI, -1.03 to -0.40) for BASFI, with an (I2) value of 0% (P<.00001) in favor of exercise. [174]

Four studies, [175, 176, 177, 180] on patients with anti-TNF-α therapy, showed a decrease of both BASDAI and BASFI with exercise. For the BASDAI, the overall WMD was -1.37 (95% CI, 1.90 to -0.84) with an I2 value of 0% (P<.00001) (Figure 2.5). For the BASFI, the WMD was -0.81 (95% CI, -1.25 to -0.38) with an I2 value of 0% (PZ.0002) (Figure 2.6). [174]

In the Fernandez et al. study, [181] the group control had a rehabilitation program supervised by a physician. Therefore, another meta-analysis excluding this study report was conducted, and the results were in the same direction. By excluding this article, no more heterogeneity was observed in a fixed effect model assessing the effect of exercise on the BASDAI (I2Z0%). [174]

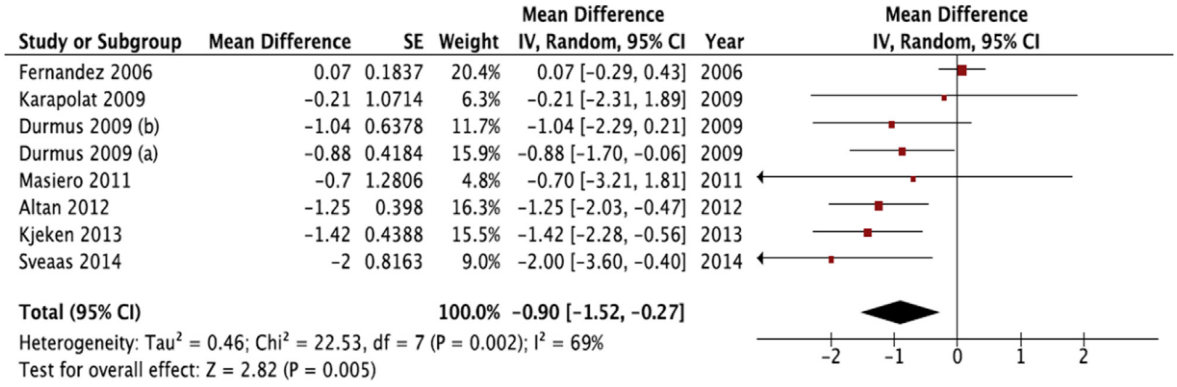

Figure 2.3 Forest plot from meta-analysis of RCTs assessing the effect of an exercise program on the BASDAI in patients with AS. IV, inverse variance model. (Pécourneau V, et al. 2017)

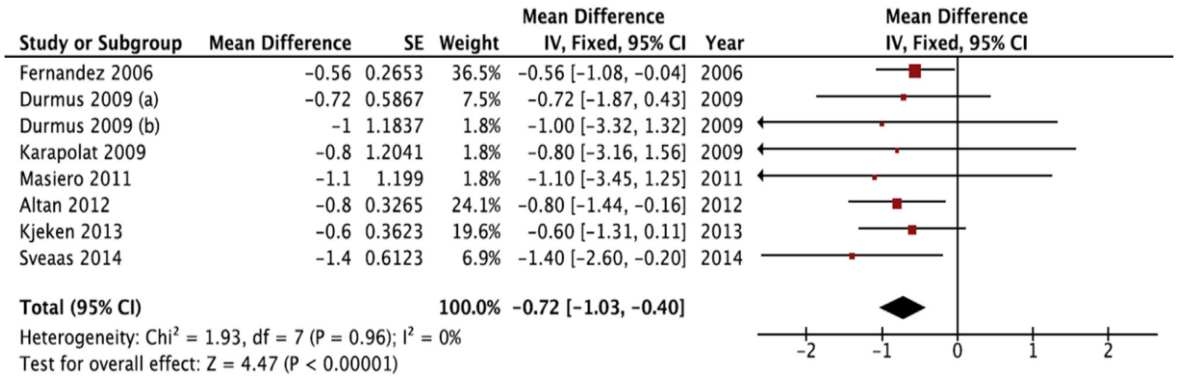

Figure 2.4 Forest plot from meta-analysis of RCTs assessing the effect of an exercise program on the BASFI in patients with AS. IV, inverse variance model. (Pécourneau V, et al. 2017)

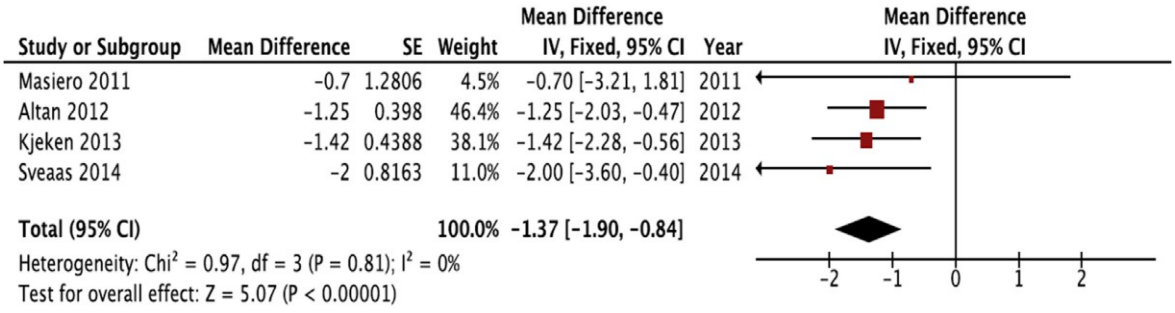

Figure 2.5 Forest plot from meta-analysis of RCTs assessing the effect of an exercise program on the BASDAI in patients with AS receiving anti-TNF-α therapy. IV, inverse variance model. (Pécourneau V, et al. 2017)

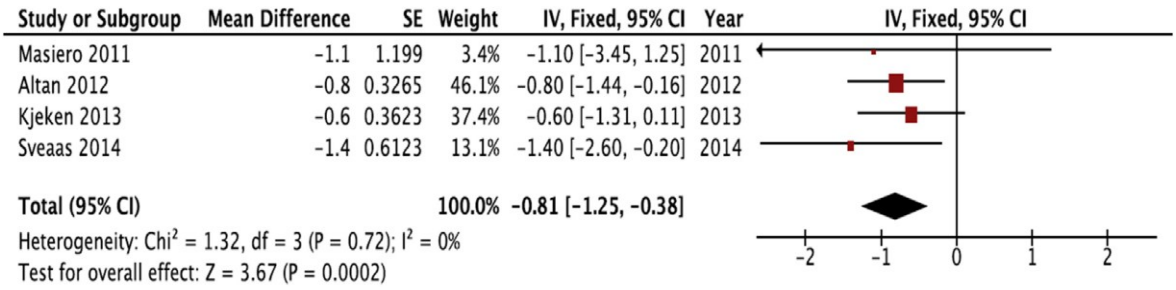

Figure 2.6 Forest plot from meta-analysis of RCTs assessing the effect of an exercise program on the BASFI in patients with AS receiving anti-TNF-α therapy therapy. IV, inverse variance model. (Pécourneau V, et al. 2017)

Pécourneau et al. found that exercise programs provided greater benefits in improving physical function and reducing disease activity compared to no intervention, with particularly strong effects observed in more recent studies that included patients receiving the anti-TNF-α treatment. [174]

Along with BASDAI reduction, exercise had a positive effect also on the BASFI in all studies. BASFI was reduced at -0.72 (95% CI, -1.03 to -0.40) overall and -0.81 (95% CI, -1.25 to -0.38) for trials with anti-TNF-α therapy, with no heterogeneity for both.

In contrast to the BASDAI, the heterogeneity for the BASFI was null, probably because this index is more stable over time. Indeed, this index specifically reflects functional impairment associated with ankylosis, which tends to worsen with disease duration.

2.3.2 Physical exercise in AS patients

The results of the meta-analysis support the previous EULAR and ACR recommendations, which emphasized the importance of exercise in decreasing disease activity and functional disability in AS.

Benefits of exercise in AS could be expected beyond disease activity and function, including CVR reduction, [182, 183] osteoporosis prevention, [184, 185] and respiratory function improvement. [186]

Firstly, patients with AS face an increased risk of cardiovascular events, including stroke and myocardial infarction. [187, 188] Aerobic exercise training is known to reduce coronary event risks in healthy individuals, [189] and a recent trial by Sveaas et al. confirmed that high-intensity aerobic and strength training can reduce cardiovascular risk factors in patients with AS. [175]

Secondly, decreased bone mineral density is a common complication in patients with long-standing AS. [190] PA has been demonstrated to prevent osteoporosis by stimulating bone formation, as well as strengthening muscles, improving balance, and reducing the overall risk of falls and fractures. [191]

Thirdly, thoracic spine involvement and enthesitis at the costosternal and manubriosternal joints can result in chest pain [192, 193] and restrictive lung disease. PA has been shown to improve vital capacity, increase forced expiratory volume, and help prevent thoracic ankylosis [194].

Four studies demonstrated a positive impact of PA on the BASDAI. Specifically, in the study by Karapolat et al. [195], PA provided notably positive results. The exercise protocol consisted in 30 minutes of freestyle swimming, plus daily flexibility and respiratory exercises for 30 minutes, 6 days a week.

Furthermore, the BASDAI was low at baseline (mean, 2.7±1.9), but its potential decrease was slight after 6 weeks of training. For the most recent studies, including patients with anti-TNF-α therapy, the reduction in BASDAI was more pronounced, with a WMD for BASDAI of -1.37 (95% CI, -1.50 to -0.84), without heterogeneity. [174]

Despite the heterogeneity of exercise protocols and outcome measures across trials in this meta-analysis, the findings support the potential benefits of exercise in improving disease activity and function in AS. Further studies are needed to establish more homogeneous exercise regimens, particularly to clarify the optimal type, frequency, and duration of effective programs. Although anti-TNF-α therapy has shown substantial effects in AS, the additional benefits of standardized, supervised exercise programs on pain, function, and quality of life require further investigation.

The ACSM [196, 197] recommends aerobic activity (walk, cycling, etc), 14-30 minutes at moderate intensity, 2-3 times per week. Strength training is also recommended 2 times per week, for 8-10 exercises, repeated 8-12 times and stretching every day.
However, based on the findings of this meta-analysis the exercises should be regular, rational, and progressive. Specific adaptations should consider AS-related limitations, such as physical capacity, joint restrictions, pain, and motivation. [195, 198] Strength training should target the weak muscle groups, especially the abdominal chain, paravertebral muscles, and iliopsoas in axial AS. [178, 179] Stretching and mobility exercises should focus on the posterior chains (hamstrings and paravertebral muscles), shoulders, and thoracic spine. [198, 199]

2.4 - The benefits of physical exercise in Psoriatic Arthritis

Unlike in RA and AS, where EULAR provides specific recommendations for PA due to its beneficial effects on disease activity and comorbidities, the latest GRAPPA guidelines for PsA do not offer explicit recommendations regarding PA. Additionally, research on PA in PsA is quite limited. However, a systematic review titled: “Psoriatic arthritis and physical activity: a systematic review” (Kessler J, et al.), was conducted on this topic by two independent readers across PubMed, Cochrane, and PEDro databases. [200]
Clinical trials assessing PA in PsA were very different, with significant variation in the types of exercise and evaluation criteria used, making global assessments and meta-analyses challenging. While the review is limited by the small number of studies and participants included, it stands out for its rigorous methodology and qualitative analysis, providing objective insights into the effects of PA on PsA. This systematic review is one of the first on this topic and it represents a valuable starting point for PA experts to encourage exercise in PsA patients.

2.4.1 Physical exercise in PsA patients

The results suggest that both aerobic (specially HIIT) and resistance training seems to have a positive impact on disease activity, on quality of life, on fatigue, on muscle strength, and partly on cardiovascular risk factors. [201] According to Roger-Silva et al., BASDAI was improved with a clinically relevant difference greater than (1.1) [202] after resistance training protocol. However, since BASDAI primarily measures axial symptoms, its relevance may be limited in patients with predominantly peripheral PsA

symptoms. Notably, recent trials demonstrated reductions in fatigue and pain by more than 15 mm on a 100 mm scale, reflecting clinically significant benefits. [203, 204]

One significant barrier to non-drug treatments like PA is adherence and compliance. Thomsen et al. has shown that the fatigue improvements observed at six months were not maintained at nine months. While the dropout rate during the unsupervised phase was low (n = 28/30), only 43% of participants reported engaging in endurance exercise during the follow-up. This underscores the importance of supervision in increasing adherence. [201]

Although no studies have evaluated the effects of PA on psoriasis in patients with PsA, a few studies have been conducted in psoriasis patients without arthritis, showing that PA is associated with a reduction in the incidence of psoriasis. [205, 206]

Thomsen et al. found that obesity, particularly abdominal obesity, is linked to an increased risk of PsA and that high intensity PA (> 1 h per week) reduces its occurrence in overweight or obese patients. [207]

Thomsen et al. also examined the effects of 11 weeks of HIIT on cardiovascular parameters, finding that VO2max, a predictor of cardiovascular health, increased significantly in the exercise group at both three and nine months (+ 3.72 ml/kg/min IC 95% 2.38 to 5.06 $p < 0.001$; +3.08 ml/kg/min IC 95% 1.63 to 4.53 $p < 0.001$). [207]

The tolerance of PA or exercise was evaluated directly during clinical trials and indirectly during retrospective studies. Clinical trials reported no adverse effects on disease activity or quality of life. In contrast, some cross-sectional studies on enthesitis risk factors have limitations. For example, according to Wervers et al. avoiding PA reduced the score for inflammatory enthesitis, [208] but this assessment primarily relied on self-reports or interviews, which are subjective. Moreover, factors like a history of enthesitis, could influence the participation of PA, complicating result interpretation. The hypothesis was that mechanical stress in an inflammatory environment promotes the onset of enthesitis. [209] Reducing the inflammatory environment with treatments could reduce the risk of enthesitis. This is why it seems necessary for patients to be in remission before starting any PA. Properly adapted and supervised exercise could also minimize this risk. [200]

In conclusion, this review highlights promising evidence supporting the benefits of PA for individuals with PsA. However, additional research is essential to strengthen and

expand these findings. The following figure (Figure 2.7) provides a summary of the effects of PA on PsA based on the results of this review. [200]

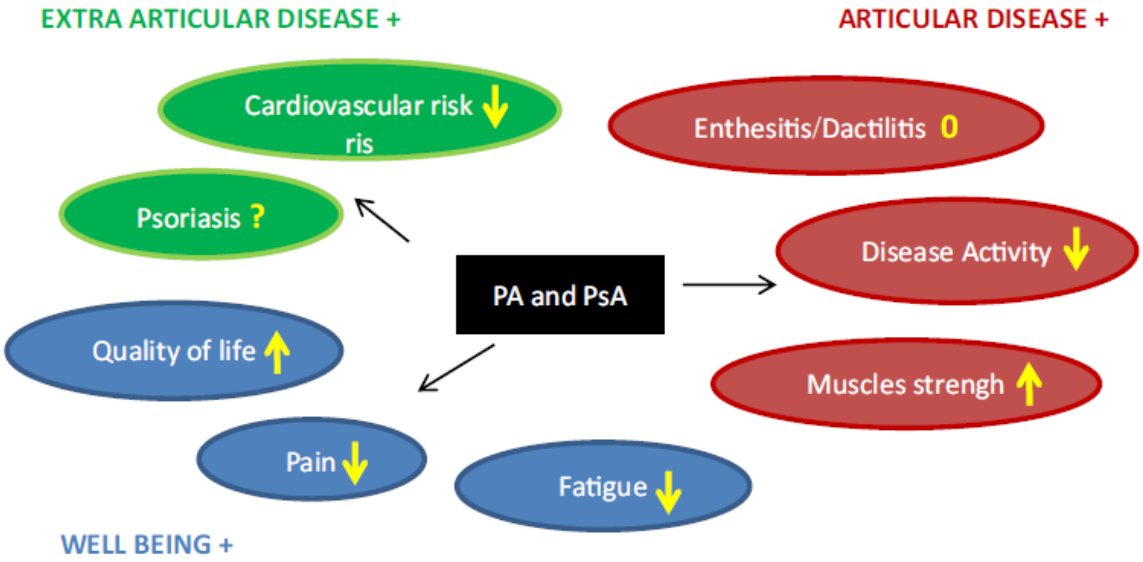

Figure 2.7 Summary of the benefits of PA in PsA patients. (Kessler J, et al. 2021)

3. EXPERIMENTAL SECTION

3.1 – Introduction

A common issue in rheumatic diseases is systemic chronic inflammation, which exposes patients to various comorbidities, reduces quality of life, and increases pain, fatigue, and stiffness. [1] The role of physical exercise in reducing inflammation in chronic diseases is well-documented in the scientific literature. [107, 108] Furthermore, some studies, particularly in RA patients, suggest that physical exercise may also reduce systemic chronic inflammation levels in rheumatic diseases. [141, 155, 160, 165]

However, the reduction in chronic inflammation is only one of the many positive effects of PA in rheumatic diseases. In conditions like RA and AS, the benefits of PA are well-supported by evidence, and the EULAR has issued specific recommendations for physical exercise in these patients. [173]

The systematic review by Hernández-Hernández et al. [140] analyzed numerous studies on the effects of PA in RA. The review showed that aerobic and resistance training, 2-3 times per week for 30-60 minutes, not only provide general health gains, but also offer disease-specific advantages such as pain reduction, improved muscle function, and delayed disability onset in RA patients. [140]

In the meta-analysis conducted by by Pécourneau et al. [174] different studies on PA in AS were analyzed. Findings indicated that PA in AS patients improves disease activity and function, as evidenced by improvements in the BASDAI scale, reduces cardiovascular risk, [182, 183] helps prevent osteoporosis, [184, 185] and enhances respiratory function. [186]

In contrast to RA and AS, where EULAR provides specific recommendations for PA and substantial evidences support its benefits, the latest GRAPPA guidelines for PsA do not offer any recommendations, and research on PA in PsA is limited. However, a systematic review by Kessler et al. [200] examined the existing literature on PA in PsA, concluding that both aerobic and strength training positively impact disease activity, quality of life, fatigue, muscle strength, some cardiovascular risk factors, and potentially even psoriasis itself.

The project, titled “Tapering of therapy: the Impact of LifesTyle and predictors of sustained remission (TILT study)”, aims to investigate the anti-inflammatory effects of physical

exercise and dietary therapy in patients with RA and SpA who are candidates for tapering biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs).

Tapering or discontinuing bDMARDs/tsDMARDs can lead to significant financial savings and reduce therapy-related side effects. [210] However, both clinicians and patients should be conscious that reducing therapy carries a risk of disease reactivation, and reliable predictors for sustained remission are currently unavailable. [211, 212]

A gradual reduction of the therapy is generally preferable to an abrupt suspension, as it is associated with a lower risk of remission loss and radiographic disease progression. [213, 214] This approach also allows clinicians to revert to the previous dose in case of relapse, while maintaining some degree of dose reduction, thus supporting a more personalized treatment strategy. [215]

Most tapering studies have focused on RA, but also research in SpA has shown good results, with tapering leading to better outcomes compare to the abrupt suspension. [216, 217] Lower disease activity before gradual therapy reduction has been associated with a reduced risk of flare in SpA, and concurrent use of conventional synthetic DMARDs (csDMARDs) has not decreased the chances of maintaining remission. [211] International recommendations for PsA suggest a cautious and gradual reduction of DMARDs for patients who have been in sustained remission for at least six months. [218] The EULAR guidelines for RA recommend that, following the discontinuation of glucocorticoids or a gradual tapering of bDMARDs or tsDMARDs may be considered if remission persists. [219] To define disease remission in PsA, indices such as the Disease Activity in Psoriatic Arthritis (DAPSA) and Minimal Disease Activity (MDA) criteria are recommended. For axSpA, the Ankylosing Spondylitis Disease Activity Score (ASDAS) is commonly used. An ASDAS score below 1.3 is suggested to assess the disease remission. [220, 221] In RA, the Boolean Remission 2.0 (B2R) criteria can be used to define disease remission. [222]

3.2 – Purpose of the study

This thesis aims to assess the initial effects of a physical exercise protocol realized by the Sport and Exercise Medicine Division of the University of Padova and held in the medical gym of the Padova University Hospital. The protocol targets patients with rheumatic diseases who were supposed to be candidates for the TILT study. Despite the TILT study is primarily focused on the anti-inflammatory effects of exercise, this thesis is just focused on the

outcomes of the first mesocycle of the protocol, representing a feasibility pilot-study preceding the whole project. Indeed, at this early stage of the physical exercise program, participants engage in low-moderate intensity exercises, in contrast with the literature recommendations, which suggest moderate to high intensity for a better anti-inflammatory effect. As a result, inflammation levels are not reported in the previous work, but will be assessed subsequently. Instead, the analysis is focused on the effects of flexibility, aerobic, and strength training on quality of life, muscular strength, aerobic capacity, balance, flexibility, and pain management.

3.3 – Materials and methods

3.3.1 Population of study

The study was conducted on the first four enrolled participants, each with a different rheumatic disease: one with RA, one with PsA, and two with AS. However, for scheduling problems, only two of these patients completed the first mesocycle of physical exercise, allowing for a pre- and post-comparison of results for these individuals. Additionally, a comparison was made across all four subjects to analyze the outcomes of the pre-test.

3.3.2 Protocol of physical exercise

The physical exercise plan was designed in accordance with literature guidelines, focused on the particular limitations belonging to RA, PsA, and AS. The first mesocycle, was composed by 10 workout sessions, prioritizing initial patient conditioning, pain management and making the patient aware about the difference between the pathological pain and the muscle soreness that can follow physical exercise.

Aerobic exercise was initially continuous, performed at a low intensity (50-60% VO_2max), and tailored to patient comfort and specific disease considerations. Participants had the option to use either a bike or a treadmill. For individuals with RA or PsA experiencing complications in the lower-limbs joints, the treadmill was avoided to reduce joint strain. Patients with AS, if comfortable, were encouraged to start on the bike and gradually move to the treadmill to improve walking biomechanics. The goal of the first mesocycle was improving or maintain aerobic condition, in order to patients to progress to higher-intensity aerobic training, such as HIIT, aimed at leveraging its anti-inflammatory benefits.

Strength training was based on multi-joint exercises using bodyweight or resistance bands, engaging all major muscle groups. Indeed, the main goal of the first mesocycle was building

strength and coordination, preparing subjects for a further increase in intensity. On the other hand, in the last mesocycle, machines like leg press and leg extension where considered, as they allow for a safer and more traceable increase in intensity. Strength exercises were selected and adapted according to the specific characteristics of each subject and their disease profile. As an example, for AS, where axial involvement is prevalent, the exercises were primarily focused on improving strength in the shoulders and core muscles. Conversely, for RA and PsA, where hand involvement is common, additional exercises to strengthen the forearms, fingers and hands muscles were incorporated into the exercise protocol.

Flexibility and mobility exercises were a central focus of the first mesocycle, as joint inflammation in rheumatic diseases often leads to restricted mobility and stiffness. Another key aim of flexibility training was to increase joint mobility for improving the quality of the movement during strength training. Although flexibility exercises targeted the entire body, specific adaptations were made for each condition. Particularly, for patients with PsA and RA, flexibility exercises for finger and wrist flexors and extensors were included. For AS, instead, exercises were tailored to improve spinal and hip mobility and were complemented by breathing exercises.

3.3.3 Testing

Subjects initially performed a maximal cardiopulmonary exercise test (CPET) conducted by a physician and aimed to determine the appropriate intensity and type of physical exercise. Subsequently, before beginning the first mesocycle, subjects were tested in the gym by a kinesiologist using specific and multi-parametric assessments described in the following sections. After completing the first mesocycle, all these tests were repeated, except the CPET, to assess the effects of the exercise protocol on participants.

CARDIO-PULMONARY EXERCISE TEST

The cardiopulmonary exercise test (CPET) is a non-invasive test that assesses the efficiency of the cardiopulmonary system and the ability of muscles to utilize peripheral oxygen during physical exercise. CPET is used to assess various parameters, including electrocardiogram (ECG), blood pressure, and peripheral oxygen saturation during an incremental and maximal physical exercise. The primary goal of CPET is to evaluate cardiopulmonary efficiency, beyond the cardiovascular response to exercise. [223] This is possible by analyzing multiple

parameters that may reveal issues in oxygen transport and utilization during physical exercise.

CPET protocols allow for evaluating the response of the body across different exercise intensities. Workloads are tailored to the individual, based on factors like age, comorbidities, weight, and the specific testing goals that the operator needs. CPET can be conducted on either a treadmill or a stationary bike. Both are effective for monitoring parameters under both maximal and submaximal exercise conditions. In this study, CPET was performed using a stationary bike with an incremental load protocol, where the resistance on the bike increased gradually while maintaining a constant pedaling rate. [224]

A CPET test is considered "maximal" if the patient reaches 85% of their maximum heart rate (HRmax) calculated for age or if the respiratory exchange ratio (RER) reaches 1.10, which was the case for the participants in this study. To measure oxygen (O_2) and carbon dioxide (CO_2) levels accurately, a mask that prevents the mixing of these two gases is used, allowing a precise calculation of the gases exchanged with each breath. [225] Oxygen saturation is monitored using a pulse oximeter, and heart rate is recorded continuously via ECG. Blood pressure is measured with a sphygmomanometer before and during the test.

During CPET the communication with patients is essential, particularly regarding any symptoms of chest pain. The operator should constantly monitor the condition of the patient for signs of distress, including shortness of breath (dyspnea), significant increases in blood pressure, ECG abnormalities, changes in skin color, and fainting. These are all critical indicators for terminating the test. [226]

The most important parameters measured in the CPET are:

-VO_2peak: This parameter is one of the most important indicators of physical exercise tolerance in a subject. It can be expressed either in absolute terms (L/min) or in relation to the body weight of the patient. [223]

-RER (Respiratory Exchange Ratio): This represents the ratio of CO_2 produced to O_2 consumed and it indicates how intense is the exercises. Indeed, as the intensity increases, the RER approaches 1, and exceeding this value it indicates that the exercise has reached the maximal intensity as previously mentioned. [227, 228]

-VAT (Ventilatory Anaerobic Threshold): This parameter reflects fitness level and is important for prescribing exercise. VAT identifies an increase in ventilation to maintain the body homeostasis due to the accumulation of lactic acid. The lactic acid produced by the

muscles during a high intensity exercise dissociates in blood in lactate and hydrogen ions lowering its pH. The CO_2 expulsion aims to decrease the blood acidosis increasing the ventilation. [229]

-HRmax (Maximum Heart Rate): is a useful marker of reaching maximal intensity, allowing a comparison between the observed heart rate and the theoretical HRmax, which is often calculated using the Cooper formula.

-O_2 Pulse: (Heart Rate $*$ Stroke Volume) / ($CaO_2 - CvO_2$). This parameter typically increases with a hyperbolic trend during exercise. An altered trend or a sudden drop during exercise may indicate a decrease in stroke volume or reduced oxygen utilization by the muscles, potentially due to a cardiovascular pathology or a severe physical deconditioning. Normally, stroke volume ranges between 90–120 mL per beat. [230]

-VE/VCO_2 Slope: This parameter is obtained by plotting VCO_2 (L/min) on the x-axis and ventilation volume (VE) on the y-axis. It assesses the efficiency of ventilation, showing how much ventilation needs to increase to expel CO_2. This slope is linear during exercise, with normal values around 23 for men and 25 for women, rising to about 28 with age.

-OUES (Oxygen Uptake Efficiency Slope): represents the relationship between inspired VO_2 and the logarithm of VE, providing an estimate of VO_2max even in submaximal conditions. [231]

-Expiratory Reserve: This is calculated as the difference between maximum VE at rest and VE during maximal effort. Expiratory reserve strongly depends on fitness level. Indeed, elite athletes may show lower values due to cardiovascular adaptations and increased oxidative capacity of mitochondria in muscles. However, a reduction in expiratory reserve in non-athletic individuals can indicate chronic obstructive pulmonary disease (COPD). [232]

SIX SENIOR FITNESS TEST BATTERY

-The **6 minutes walking test** consists in walking on a straight and flat corridor for six minutes and measure the distance covered by the participant within that time. This test was used to estimate the aerobic capacity and endurance of subjects under submaximal conditions. During the test, the operator monitors the subject to ensure a correct performance and, eventually, provides assistance if necessary. At the end of the test, the operator assesses the fatigue level of the participant using the 6–20 Borg Scale. [233]

-The **30 seconds chair stand test** involves the subject repeatedly rising from a chair and sitting back down on it for 30 seconds, in order to complete as many repetitions as possible within that time. The starting position is seated, with arms crossed over the chest. A repetition is counted each time the participant fully rises, achieving both hips and knees joints extension, and then returns to a seated position. This test evaluates strength and endurance of the lower-limbs. [234]

-The **8-foot up & go test** consist in standing up from a chair positioned near a wall for guarantee stability, walking quickly (but not running) to a cone placed 8 feet away, and returning to the chair. This test was conducted to assess agility and balance. Upon receiving the "go" signal from the operator, the participant stands up without using the arms for assistance, walks to the cone, turns, and returns to the chair. The timer stops once the participant is seated again. The test includes three trials. [235]

-The **arm curl test** is designed to evaluate upper-limbs strength and endurance, specifically targeting the biceps muscle. The participant sits holding a dumbbell (2 kg for women and 3 kg for men) and performs as many curls as possible within 30 seconds. During each repetition, a fully extension and flexion of the arm is required. The test is conducted for both arms, and an average score is calculated between the two limbs. [235]

-The **sit & reach test** was conducted with the subject seated in a chair, extending one leg at a time and attempting to reach maximum hip flexion by reaching the toes with the hands. The same procedure was repeated for the opposite leg. The distance between the fingertips and the toes was recorded to assess the flexibility of the posterior chain. [235]

-The **back scratch test** was conducted in a standing position. The operator instructed the participant to place the right arm in a fully flexed and external rotated position overhead, while positioning the left arm in a fully extended and internal rotated position behind the back. The test was then repeated with the arms in the opposite positions. The distance between the fingertips of each hand was measured to assess the upper-limbs flexibility. [235]

SHORT PHYSICAL PERFORMANCE BATTERY

The Short Physical Performance Battery (SPPB) test was administered to assess three components: balance, walking ability, and lower-limbs strength. [236]

-Balance component: The participant maintains different standing positions, with each position increasing in difficulty from the first to the last. [236]

-Walking component: The participant walks a 4-meter distance as quickly as possible but without running. This component is repeated twice, and the best time is recorded. [236]

-Strength component: The participant performs five chair squats, starting and ending seated with arms crossed over the chest, performing a full knees and hips extension on each repetition. [236]

Each component is scored from 0 to 4, with higher scores indicating better performance. The total SPPB score, calculated by summing all component scores, ranges from 4 to 12. Scores of 4-6 indicate low performance, 7-9 indicate moderate performance, and 10-12 indicate high performance, based on established clinical benchmarks. [236]

ISOMETRIC AND ISOKINETIC TESTS

An isometric and isokinetic test of knee flexion and extension was conducted to assess lower-limbs strength. The tests was conducted using an isokinetic dynamometer (Prima Plus, Easytech, Italy), which measures knee flexion and extension as well as ankle dorsiflexion and plantarflexion in a seated position. However, only knee flexion and extension were evaluated in this study. For the isometric test, the knee was positioned at 75° of flexion, and each contraction lasted 5 seconds. For the isokinetic test, knee flexion and extension were performed at an angular velocity of 60°/s. [237]

HANDGRIP TEST

The handgrip test was conducted to evaluate grip strength in both the dominant and non-dominant hands. Participants performed the test with their elbow flexed at a 90° angle using a hydraulic hand dynamometer (Baseline® Evaluation Instruments, Elmsford, NY, USA). Three trials were performed for each hand, and the mean of these trials was calculated to determine the percentile ranking for each participant according to the normative values established in “New Normative Values for Handgrip Strength: Results from the UK Biobank”. [238]

ANGULAR MEASUREMENTS

In addition to the sit & reach and the back scratch tests, joint flexibility was specifically evaluated at the ankle, hip, and shoulder joints. Indeed, active range of motion angles for

ankle plantarflexion and dorsiflexion, hip flexion, and shoulder flexion were measured using a universal goniometer. [239]

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

The International Physical Activity Questionnaire (IPAQ) was administered and interpreted by the operator to estimate the level of physical activity for each participant. The interpretation was based on the total weekly time (minutes) reported with the intensity of the PA, which was converted into metabolic equivalents (METs). Participants were classified as inactive if their PA was below 700 METs*min/week, sufficiently active if between 700 and 2519 METs*min/week, and active or very active if at or above 2520 METs*min/week. [240]

MEDICAL OUTCOMES SHORT FORM 36 QUESTIONNAIRES

The Medical Outcomes Short Form 36 questionnaire (SF-36) was administered to assess the quality of life. Each participant received a copy to complete at home. The questionnaire consists in 36 items evaluating self-perceived functional status, well-being, and overall health. The items were added together and translated into a final score for each component, ranging from 0 (indicating the poorest health) to 100 (representing optimal health). [241]

3.3.4 Data collection and analysis

Due to the limited number of subjects and time constraints, a full statistical analysis was not feasible for this study. Instead, data analysis focused on calculating the mean and standard deviation of baseline test results across the four participants. Additionally, a comparative analysis was performed on the pre- and post-test results for the two subjects who completed the first mesocycle of adapted physical exercise. All data were collected and analyzed using Excel sheets.

3.4 – Results

Subjects underwent a CPET before starting the physical exercise program. The exercise prescription was tailored based on the results of the CPET. All four participants were male, with an average age of 48 years, an average height of 182 cm, and an average weight of 84,5 kg. Participants showed normal or mildly reduced functional capacity (Table 3.1).

CPET	SUBJECTS (PRE)				MEAN	S.DEV
	T001	T002	T003	T004		
VO_2 peak (ml/kg/min)	29,9	26,8	24,2	32,6	28,4	3,7
VO_2 peak (L/min)	2,633	1,981	2,255	2,706	2,394	0,339
%VO_2 predicted	78	88	78	114	89,5	17,0
AT1_%VO_2peak	61	54	60	51	56,5	4,8
AT2_%VO_2peak	84	89	82	83	84,5	3,1
AT1_VO_2 (ml/min)	18,1	14,4	14,6	16,8	16,0	1,8
AT2_VO_2 (ml/min)	25,1	23,8	19,9	26,9	23,9	3,0
AT1_%FC max	75	72	74	62	70,8	6,0
AT2_%FC max	91	96	93	84	91,0	5,1
AT1_FC (bpm)	136	113	122	106	119,3	12,9
AT2_FC (bpm)	164	151	153	144	153,0	8,3
RER rest	0,76	0,85	0,9	0,79	0,83	0,06
RER max	1,11	1,1	1,1	1,19	1,13	0,04
VE/VCO_2 slope	18,97	27,74	24,01	28,82	24,89	4,45
FC max (bpm)	181	157	164	171	168,3	10,2
%FC max predicted	97	96	93	104	97,5	4,7
$PETCO_2$ rest (mmHg)	38,73	35,21	35,01	33,86	35,70	2,10
$PETCO_2$ apex (mmHg)	50,82	39,52	40,86	38,22	42,36	5,75
Delta $PETCO_2$	31,21	12,24	16,71	12,87	18,26	8,86
O_2 pulse peak (ml/beat)	14,5	12,6	13,7	16	14,2	1,4
% O_2 Pulse predicted	79	91	83	111	91,0	14,2
Plateau O_2 Pulse	linear	linear	linear	linear	-	-
% Breath Reserve	62	49	50	11	43,0	22,1
% Sp O_2 peak	99	98	99	99	98,8	0,5
%Vd/Vt	18	18	17	19	18,0	0,8
FR resp max (breath/min)	36	29	27	48	35,0	9,5
OUESs (ml/min/log10)	3201,98	2377,57	2427,43	2904,95	2727,98	395,44

Table 3.1 Main parameters assessed during the CPET. With the comparison in terms of mean and standard deviation within the first four enrolled participants: T001, T002, T003 and T004.

The following list provides the definition of the acronyms used to describe the parameters evaluated during the CPET (Table 3.1):

-VO_2 peak (ml/kg/min): relative maximum oxygen uptake;

-VO_2 peak (L/min): absolute maximum oxygen uptake;

-%VO_2 predicted: percentage of the predicted VO_2 max;

-AT1_%VO_2peak: percentage of VO_2 peak at the first anaerobic threshold;

-AT2_%VO_2peak: percentage of VO_2 peak at the second anaerobic threshold;

-AT1_VO_2 (ml/min): oxygen uptake at the first anaerobic threshold;

-AT2_VO_2 (ml/min): oxygen uptake at the second anaerobic threshold;

-AT1_%FCmax: percentage of maximum heart rate at the first anaerobic threshold;

-AT2_%FCmax: percentage of maximum heart rate at the second anaerobic threshold;

-AT1_FC (bpm): heart rate at the first anaerobic threshold;

-AT2_FC (bpm): heart rate at the second anaerobic threshold;

-FC max (bpm): maximum assessed heart rate,

-%FC max predicted: percentage of the maximum predicted heart rate;

-RER rest: respiratory exchange ratio (CO_2 produced/O_2 consumed) at rest;

-RER max: maximum RER achieved during exercise;

-VE/VCO_2 slope: relationship between ventilation (VE) and CO_2 production (VCO_2);

-$PETCO_2$ rest (mmHg): partial pressure of end-tidal CO_2 at rest;

-$PETCO_2$ apex (mmHg): partial pressure of end-tidal CO_2 at peak exercise;

-Delta $PETCO_2$: difference between end-tidal CO_2 pressure at rest and at peak exercise;

-O_2 pulse peak (ml/beat): oxygen uptake per heartbeat at peak exercise;

-%O_2 Pulse predicted: percentage of the predicted O_2 pulse;

-Plateau O_2 Pulse: trend of O_2 pulse during exercise;

-%Breath Reserve: percentage of ventilatory reserve;

-%SpO_2 peak: percentage of oxygen saturation at peak exercise;

-%Vd/Vt: relationship between the physiological dead space and tidal volume;

-FR resp max (breaths/min): maximum respiratory rate;

-OUES: oxygen uptake efficiency slope.

No significant abnormalities were observed among the four patients. All participants achieved maximal effort during the CPET, as evidenced by a respiratory exchange ratio (RER) ≥ 1.0. The VE/VCO2 slope was within the normal range for all patients, except for

patient T001, whose value was slightly below normal. Peak O2 pulse values were normal, and the O2 pulse plateau was linear for all participants, indicating no signs of cardiovascular disease. Notably, patient T004 was highly physically active, as reflected by several parameters differing significantly from those of the other three participants (Table 3.1).

SIX SENIOR FITNESS TEST BATTERY		SUBJECTS (PRE)				MEAN	S.DEV
		T001	T002	T003	T004		
6-MINUTE WALKING TEST	Distance (m)	588	562	561	538	562,3	17,7
	Borg	11	11	10	9	10,3	0,8
30 SECONDS CHAIR STAND TEST	Repetitions (n)	13	16	15	15	14,8	1,1
8 FOOT UP & GO	1st trial (sec)	4,32	4,33	5,18	5,57	4,85	0,54
	2nd trial (sec)	3,96	4,14	5,57	5,13	4,70	0,67
	3rd trial (sec)	4,08	4,14	4,19	4,9	4,33	0,33
ARM CURL TEST	Repetitions right arm (n)	23	29	21	21	23,5	3,3
	Repetitions left arm (n)	23	25	21	18	21,8	2,6
	Mean (cm)	23	27	21	19,5	22,6	2,8
BACK SCRATCH TEST	Right arm trial (cm)	4	-8	-13	4	-3,3	7,5
	Left arm trial (cm)	5	-14	-13,5	6	-4,1	9,6
	Mean (cm)	4,5	-11	-13,25	5	-3,7	8,5
SIT&REACH TEST	Right leg trial (cm)	10	-8	4,5	-6	0,1	7,4
	Left leg trial (cm)	-1	-9	-6,5	-4	-5,1	3,0
	Mean (cm)	4,5	-8,5	-1	-5	-2,5	4,8

Table 3.2 Six senior fitness battery, including all the results of the pre-tests and the comparison in terms of mean and standard deviation across the first four enrolled participants: T001, T002, T003 and T004.

In the Senior Fitness Battery, all participants showed similar results in the strength and endurance tests, as they were generally inactive or only minimally active, with the exception of T004. However, flexibility assessments revealed that T003 and T004 had poorer mobility in the back scratch and sit and reach tests, whereas T001 and T003 exhibited better outcomes in these components. (Table 3.2)

SPPB		SUBJECTS (PRE)				MEAN	S.DEV
		T001	T002	T003	T004		
BALANCE	Score	4	4	4	4	4	0
WALKINKG ABILITY	Score	4	4	4	4	4	0
LOWER LIMBS STRENGTH	Score	4	4	4	4	4	0
SCORE	Total	12	12	12	12	12	0

Table 3.3 Short Physical Performance Battery, including all the results of the pre-tests and the comparison in terms of mean and standard deviation between the first four enrolled participants: T001, T002, T003 and T004.

All subjects achieved the maximum score in each component of the SPPB, resulting in a perfect total score. (Table 3.3)

ANGULAR MESURMENTS		SUBJECTS (PRE)				MEAN	S.DEV
		T001	T002	T003	T004		
ANKLE	Plantar flexion right foot (°)	52	54	46	31	45,8	10,4
	Dorsiflexion right foot (°)	26	16	14	20	19,0	5,3
	Plantar flexion left foot (°)	62	40	40	44	46,5	10,5
	Dorsiflexion left foot (°)	20	18	8	21	16,8	6,0
HIP	Right hip flexion (°)	112	121	112	128	118,3	7,8
	Left hip flexion (°)	108	116	112	128	116,0	8,6
SHOULDER	Right arm flexion (°)	160	162	152	200	168,5	21,4
	Left arm flexion (°)	162	160	150	190	165,5	17,2

Table 3.4 Angular measurements of ankle, hip and shoulder. Including all the results of the pre-tests and the in terms of mean and standard deviation across the first four enrolled participants: T001, T002, T003 and T004.

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The angular measurements are highly operator-dependent, resulting in variability and reduced precision. This poses a limitation when using these tests to assess joint flexibility. (Table 3.4)

LOWER LIMBS STRENGTH TESTS		SUBJECTS (PRE)				MEAN	S.DEV
		T001	T002	T003	T004		
ISOMETRIC TESTS (KNEES)	Mean max isometric extension torque 1st, 2nd trials (Nm)	454,5	311	377,5	474	404,3	74,8
	Mean isometric extension torque 1st trial (Nm)	375	264	315	449	350,8	79,7
	Mean isometric extension torque 2nd trial (Nm)	444	289	327	433	373,3	77,1
	Amount of work 1st trial (J)	1893	1332	1591	2266	1770,5	402,1
	Amount of work 2nd trial (J)	2241	1461	1651	2200	1888,3	391,8
ISOKINETIC TESTS (KNEES)	Mean peak extension torque 1st, 2nd trials (Nm)	279,5	183	201,5	206	217,5	42,5
	Mean peak flexion torque 1st, 2nd trials (Nm)	164	128,5	69,5	74	109,0	45,4
	Mean peak extension 1st trial (Nm)	252	171	142	132	174,3	54,4
	Mean peak flexion 1st trial (Nm)	136	115	45	44	85,0	47,5
	Mean peak extension 2nd trial (Nm)	263	181	216	225	221,3	33,7
	Mean peak flexion 2nd trial (Nm)	170	115	64	76	106,3	47,8
	Mean max power extension 1st, 2nd trials (W)	486,5	304,5	336,5	345,5	368,3	80,8
	Mean max power flexion 1st, 2nd trials (W)	307,5	224	111	118,5	190,3	93,7
	Mean ratio F/E	58	69,5	34,5	35,5	49,4	17,3

Table 3.5 Isometric and isokinetic knees tests. Assessing the lower-limbs strength. Including all the results of the pre-tests and the comparison in terms of mean and standard deviation across the first four enrolled participants: T001, T002, T003 and T004.

Lower-limbs strength and power varied significantly among the subjects, probably due to differences in body weight age and PA levels. An isometric test was performed to evaluate the isometric strength of knee extensors, while an isokinetic test assessed the strength and

power of both knee extensors and flexors. Additionally, the flexor/extensor ratio was calculated during the isokinetic test (Table 3.5).

HANDGRIP TEST	SUBJECTS (PRE)				MEAN	S.DEV
	T001	T002	T003	T004		
Dominant arm	dx	dx	dx	dx	-	-
1st trial right arm (kg)	46	50	52	50	49,5	2,5
1st trial left arm (kg)	50	46	50	46	48,0	2,3
2nd trial right arm (kg)	52	48	53	46	49,8	3,3
2nd trial left arm (kg)	46	48	46	42	45,5	2,5
3rd trial right arm (kg)	50	46	51	42	47,3	4,1
3rd trial left arm (kg)	52	46	47	38	45,8	5,8
Mean right arm (kg)	49,3	48	52	46	48,8	2,5
Percentiles right arm (°)	50	75	75	50	-	-
Mean left arm (kg)	49,3	46,7	47,7	42	46,4	3,1
Percentiles left arm (°)	50	75	75	50	-	-

Table 3.6 Handgrip test, including all the results of the pre-tests and the comparison in terms of mean and standard deviation within the first four enrolled participants: T001, T002, T003 and T004.

Grip strength was assessed using the handgrip test. No significant differences were observed among the subjects. Three trials were conducted for each hand, and the average of these trials was calculated to determine the percentile ranking for each participant. T001 and T004 were placed in the 50° percentile, while T002 and T003 ranked in the 75° percentile (Table 3.6).

QUESTIONNAIRE		SUBJECTS (PRE)				MEAN	S.DEV
		T001	T002	T003	T004		
IPAQ	METS*min/week	690	1140	282,5	3360	1368,1	1373,3
	Interpretation	inactive	moderate active	inactive	very active	-	-
SF-36	Physical Activity (PF)	29	28	28	30	28,8	1,0
	Role physical (RP)	8	8	6	8	7,5	1,0
	Bodily pain (BP)	11	6	9	9	8,8	2,1
	General health (GH)	12	19	15	23	17,3	4,8
	Vitality (VT)	14	15	15	22	16,5	3,7
	Social functioning (SF)	8	9	6	10	8,3	1,7
	Role emotional (RE)	4	6	4	6	5,0	1,2
	Mental health (MH)	22	23	20	29	23,5	3,9
	Physical Component Summary (PCS)	60	61	58	70	62,3	5,3
	Mental Component Summary (MCS)	48	53	45	67	53,3	9,7

Table 3.7 International Physical Activity Questionnaire and Medical Outcomes Short Form 36 questionnaire, including all the results of the pre-tests and the comparison in terms of mean and standard deviation across the first four enrolled participants: T001, T002, T003 and T004.

As previously mentioned, subject T004 was very active compared to the other participants, as reflected the IPAQ questionaries, which recorded an amount of METS*min/week of 3360. Contrary, T001 and T003 subjects were very inactive, while T002 subject was moderate active with 1140 METS*min/week (Table 3.7).

Similarly, in the SF-36 assessment, T004 subject had the best outcomes both in the PCS and in MCS, likely due to a higher level of PA compare to the other threes, which did not show significant changes in scores (Table 3.7).

Subjects T004 and T003 successfully completed the first mesocycle of physical exercise. Consequently, all tests (excluding the CPET) were repeated allowing a comparison between pre- and post-intervention results.

SIX SENIOR FITNESS TEST BATTERY		SUBJECT T004			SUBJECT T003		
		PRE	POST	Δ%	PRE	POST	Δ%
6-MINUTE WALKING TEST	Distance (m)	538	614	14%	561	668	19%
	Borg	9	9	0%	10	12	20%
30 SECONDS CHAIR STAND TEST	Repetitions (n)	15	18	20%	15	18	20%
8 FOOT UP & GO	1st trial (sec)	5,57	4,22	-24%	5,18	3,97	-23%
	2nd trial (sec)	5,13	4,15	-19%	5,57	3,98	-29%
	3rd trial (sec)	4,9	3,19	-35%	4,91	3,99	-19%
ARM CURL TEST	Repetitions right arm (n)	21	26	24%	21	23	10%
	Repetitions left arm (n)	18	26	44%	21	21	0%
	Mean (cm)	19,5	26	33%	21	22	5%
BACK SCRATCH TEST	Right arm trial (cm)	4	10	150%	-13	-27	-108%
	Left arm trial (cm)	6	8	33%	-13,5	-27	-100%
	Mean (cm)	5	9	80%	-13,3	-27	-104%
SIT&REACH TEST	Right leg trial (cm)	-6	0	100%	4,5	8,5	89%
	Left leg trial (cm)	-4	3	175%	-6,5	-6,5	0%
	Mean (cm)	-5	1,5	130%	-1	1	200%

Table 3.8 Six senior fitness battery: comparison between pre and post-test in T003 and T004 subjects.

Both subjects, T004 and T003, showed improvements in the 6-minute walking test, with particularly notable progress observed in T003. This outcome was expected, given the low baseline activity level reported for subject T003 before starting the physical exercise protocol (Table 3.8).

A 20% increase was observed in the 30-second chair stand test for both participants, indicating an increasing in lower-limbs strength and endurance (Table 3.8).

However, the 8 foot up & go test showed no improvement. Indeed, post-intervention results were worse for both participants (Table 3.8).

Upper-limbs strength demonstrated significant improvement, especially for T004, who achieved a 33% increase in repetitions during the arm curl test (Table 3.8).

In terms of flexibility, T004 achieved considerable progress in both the back scratch test and the sit & reach test, suggesting an increase in flexibility in the shoulders and posterior chain. Conversely, T003 showed a decline in the back scratch test but achieved a positive outcome in the sit & reach test, particularly with the right leg (Table 3.8).

SPPB		SUBJECT T004			SUBJECT T003		
		PRE	POST	Δ%	PRE	POST	Δ%
BALANCE	Score	4	4	0%	4	4	0%
WALKINKG ABILITY	Score	4	4	0%	4	4	0%
LOWER LIMBS STRENGTH	Score	4	4	0%	4	4	0%
SCORE	Total	12	12	0%	12	12	0%

Table 3.9 Short Physical Performance Battery: comparison between pre and post-test in T003 and T004 subjects.

In the SPPB, all participants achieved the maximum score across all three components in both the pre- and post-tests. Consequently, no improvements or declines were observed in the comparison (Table 3.9).

ISOMETRIC TESTS (KNEES)	SUBJECT T004			SUBJECT T003		
	PRE	POST	Δ%	PRE	POST	Δ%
Max isometric extension torque 1st trial (Nm)	484	474	-2%	363	428	18%
Max isometric extension torque 2nd trial (Nm)	464	458	-1%	392	440	12%
Mean max isometric extension torque (Nm)	474	466	-2%	377,5	434	15%
Mean isometric extension torque 1st trial (Nm)	449	445	-1%	315	363	15%
Mean isometric extension torque 2nd trial (Nm)	433	435	0%	327	383	17%
Ammount of work 1st trial (J)	2266	2246	-1%	1591	1833	15%
Ammount of work 2nd trial (J)	2200	2175	-1%	1651	1934	17%

Table 3.10 Isometric knees tests: comparison between pre and post-test in T003 and T004 subjects.

No significant changes in strength were observed in subject T004 during the isometric tests. However, subject T003 demonstrated notable improvements (Table 3.10).

ISOKINETIC TESTS (KNEES)	SUBJECT T004			SUBJECT T003		
	PRE	POST	Δ%	PRE	POST	Δ%
Peak extension torque 1st trial (Nm)	170	215	26%	166	250	51%
Peak extension torque 2nd trial (Nm)	242	252	4%	237	257	8%
Mean extension torque (Nm)	206	233,5	13%	201,5	253,5	26%
Peak flexion torque 1st trial (Nm)	58	101	74%	66	80	21%
Peak flexion torque 2nd trial (Nm)	90	112	24%	73	87	19%
Mean flexion torque (Nm)	74	106,5	44%	69,5	83,5	20%
Mean peak extension 1st trial (Nm)	132	163	23%	142	214	51%
Mean peak flexion 1st trial (Nm)	44	66	50%	45	71	58%
Mean peaks extension 2nd trial (Nm)	225	246	9%	216	247	14%
Mean peaks flexion 2nd trial (Nm)	76	110	45%	64	91	42%
Max power extension 1st trial (W)	278	363	31%	270	434	61%
Max power flexion 1st trial (W)	88	170	93%	103	133	29%
Max power extension 2nd trial (W)	413	442	7%	403	448	11%
Max power flexion 2nd trial (W)	149	191	28%	119	169	42%
F/E ratio (%) 1st trial	34	46	35%	39	32	-18%
F/E ratio (%) 2nd trial	37	44	19%	30	37	23%
Mean ratio F/E	35,5	45	27%	34,5	34,5	0%

Table 3.11 Isokinetic knees tests: comparison between pre and post-test in T003 and T004 subjects.

Both strength and power increased in the participants in the isokinetic test, particularly in the knee flexors. This can be explained because these muscles are less utilized in daily activities, making them more responsive to strength training. In subject T004, who was already highly active with activities such as running and cycling, the flexor/extensor ratio

showed improvement. This can be attributed to the fact that in this subject the extensor strength was more developed due to his usual activities. After the first mesocycle, which also targeted the knee flexors, a better balance in muscle strength was achieved (Table 3.11).

HANDGRIP TEST	SUBJECT T004			SUBJECT T003		
	PRE	POST	Δ%	PRE	POST	Δ%
Dominant arm	dx		-	dx		-
1st trial right arm (kg)	50	49	-2%	52	53	2%
1st trial left arm (kg)	46	46	0%	50	50	0%
2nd trial right arm (kg)	46	51	11%	53	55	4%
2nd trial left arm (kg)	42	45	7%	46	49	7%
3rd trial right arm (kg)	42	51	21%	51	56	10%
3rd trial left arm (kg)	38	45	18%	47	49	4%
Mean right arm (kg)	46	50,3	9%	52	54,6	5%
Percentiles right arm (°)	50	75	-	75	90	-
Mean left arm (kg)	42	45,3	8%	47,7	49,3	3%
Percentiles left arm (°)	50	75	-	75	75	-

Table 3.12 Handgrip test: comparison between pre and post-test in T003 and T004 subjects.

After the first physical exercise mesocycle, a slight increase in grip strength was observed. It is important to note that both T004 and T003 were subjects with AS, and their exercise protocol did not include specific hand-strengthening exercises that could significantly enhance grip strength. Therefore, this increase can be attributes to adaptations during other upper body strength exercises, particularly rows (Table 3.12).

ANGULAR MESURMENTS		SUBJECT T004			SUBJECT T003		
		PRE	POST	Δ%	PRE	POST	Δ%
ANKLE	Plantar flexion right foot (°)	31	54	74%	46	65	41%
	Dorsiflexion right foot (°)	20	10	-50%	14	10	-29%
	Plantar flexion left foot (°)	44	70	59%	40	40	0%
	Dorsiflexion left foot (°)	21	14	-33%	8	12	50%
HIP	Right hip flexion (°)	128	132	3%	112	120	7%
	Left hip flexion (°)	128	136	6%	112	120	7%
SHOULDER	Right arm flexion (°)	200	180	-10%	150	150	0%
	Left arm flexion (°)	190	180	-5%	150	150	0%

Table 3.13 Angular measurements: comparison between pre and post-test in T003 and T004 subjects.

Ankle plantar flexion and hip flexion improved in both subjects. However, no significant changes were observed in shoulder flexion, and a decrease in ankle dorsiflexion was recorded in both participants. The limitation of these tests was that different operators conducted the pre-test and post-test, which leads to repeatability errors (Table 3.13).

QUESTIONNAIRE		SUBJECT T004			SUBJECT T003		
		PRE	POST	Δ%	PRE	POST	Δ%
IPAQ	METS*min/week	3360	2880	-14%	282,5	480	70%
	Interpretation	very active	very active	-	inactive	inactive	-
SF-36	Physical Functioning (PF)	30	30	0%	28	28	0%
	Role physical (RP)	8	8	0%	6	8	33%
	Bodily pain (BP)	9	10	11%	9	9	0%
	General health (GH)	23	21	-9%	15	15	0%
	Vitality (VT)	22	24	9%	15	13	-13%
	Social functioning (SF)	10	10	0%	6	8	33%
	Role emotional (RE)	6	6	0%	4	6	50%
	Mental health (MH)	29	30	3%	20	22	10%
	Physical Component Summary (PCS)	70	69	-1%	58	60	3%
	Mental Component Summary (MCS)	67	70	4%	45	49	9%

Table 3.14 International Physical Activity Questionnaire and Medical Outcomes Short Form 36 questionnaire: comparison between pre and post-test in T003 and T004 subjects.

Subject T004 already had a high level of PA before starting the exercise plan, while subject T003 was considered very inactive. Although the METS*min/week value remained below the threshold for being classified as "active," subject T003 showed a substantial 70% increase in METS*min/week from pre- to post-tests (Table 3.14).

In the SF-36 results, subject T004 showed no significant change in PCS score, however a 4% improvement in MCS was recorded. Conversely, subject T003 showed improvements in both PCS and, more notably, in MCS, reflecting positive changes in perceived mental health (Table 3.14).

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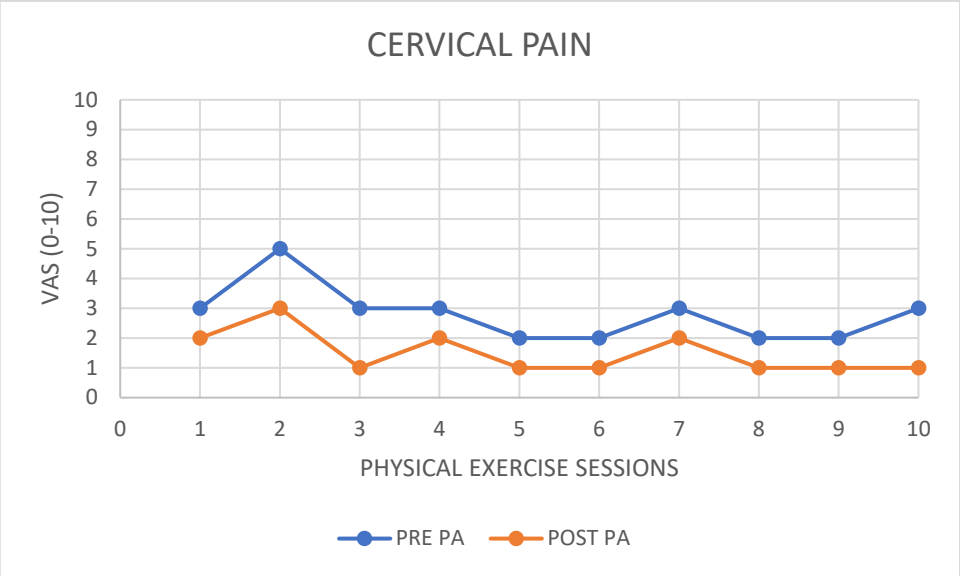

Figure 3.1 Cervical pain trend throughout the ten exercise sessions measured with VAS in subject T004

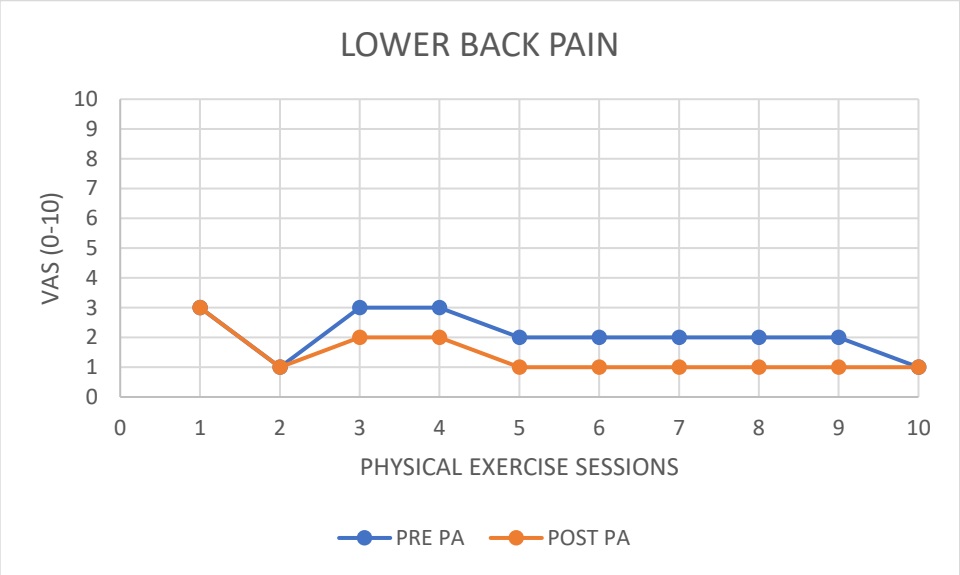

Figure 3.2 Lower back pain trend throughout the ten exercise sessions measured with VAS in subject T004

Additionally, two graphs (Figures 3.1 and 3.2) were realized to analyze the pain trend during the ten exercise sessions for subject T004. This subject was chosen because of persistent pain in the neck and lower back, which was reported during both the pre- and post-tests. However, as shown in the graphs, pain in both the neck and lower back decreased progressively from the first to the last session, with a clear difference observed between pre- and post-session pain levels. This trend underscores the effectiveness of the exercise protocol in alleviating both acute and chronic pain.

3.5 – Discussion

Before implementing a physical exercise plan, is essential to conduct pre-tests and post-tests. These tests are necessary to evaluate the baseline condition of the participants, managing exercise prescription, and assess the effectiveness of the protocol in achieving improvements. In this study, the chosen tests were suitable for evaluating different outcomes with a reasonable degree of precision, although some limitations were identified.

The cardiopulmonary exercise test (CPET) is probably the most reliable test and was essential for tailoring the prescription of physical exercise. [223, 224, 225]

Tests such as the Senior Fitness Test battery, SPPB, handgrip test, and isometric and isokinetic tests were reliable as well. [233, 234, 235, 236, 237, 238] Indeed, they assessed improvements in strength, flexibility, endurance, and balance showing trustable results for evaluating physical changes after the exercise program.

However, angular measurements and questionnaires were affected by limitations. [239, 240, 241] The angular measurements, as shown in the results, did not provide consistent outcomes. A key issue was the involvement of different operators for the pre-tests and post-tests, which inevitably leads to repeatability errors. This limitation could be easily avoided by ensuring the same operator conducts all angular measurements.

Regarding questionnaires, IPAQ was administered under operator supervision to minimize errors, as participants might misjudge the quantity of their physical activity. Although IPAQ gives just an estimation of the actual level of physical activity it remains a valuable tool for this purpose. [240] Similarly, the SF-36 questionnaire is an effective method for assessing the health status and quality of life of subjects. However, since it relies on self-reported data, it only provides an estimation and may not fully reflect the actual condition of the participants. [241]

The physical exercise protocol showed positive outcomes after the first mesocycle, which focused on low intensity and volume. These initial adaptations suggest that with the second and third mesocycles, by progressively increasing intensity and volume, further improvements in strength, flexibility, and endurance may be observed.

Both upper- and lower-limbs strength increased after the first mesocycle, as demonstrated in post-test results. Nevertheless, increases in aerobic capacity could not be correctly assessed using the 6-minute walking test alone. While this test provides a general indication of aerobic

capacity improvements, it is not as precise as a post CPET would be. However, in the absence of a follow-up with CPET, the walking test can be useful for this purpose. [233]

Flexibility improvements were significant, particularly in the back scratch and sit and reach tests. This is crucial for individuals with rheumatic diseases, indeed a reduction in flexibility and joint stiffness are common symptoms related to pain and chronic inflammation. [1, 140, 173, 174, 200] Additionally, improving flexibility had a secondary purpose in the first mesocycle. An increase in flexibility enhances performance in strength exercises by allowing subjects to work through a full range of motion, which may contribute to further strength gains in subsequent mesocycles.

A limitation of the exercise plan was the lack of standardization. Indeed, each protocol was tailored based on the specific condition of the subject, joint pain, physical limitations, and PA levels. While customized exercise protocols are essential for achieving optimal outcomes, a standardized protocol is necessary for comparing the effects of physical exercise across larger groups.

Managing pain caused by chronic inflammation is a crucial aspect in rheumatic diseases. [1, 140, 173, 174, 200] For subject T004, pain levels modestly decreased from the first to the final session, as measured using the VAS scale before and after each session. Participants also maintained a diary to record joint-specific pain, again using the VAS scale, the day after each session. Both subjects T004 and T003 did not reported an increasing in pain, suggesting that the proposed exercise protocols were both safe and effective.

Notably, subject T004 experienced a complete resolution of lower back pain during the night, a common symptom of inflammatory diseases, [1] by the end of the first mesocycle. This improvement contributed to better sleep quality, as reported by the subject. Similarly, subject T001, referred a progressive decrease in lower back pain followed by each session.

These results underline the role of physical exercise not only in improving physical function but also in reducing pain and enhancing the quality of life for individuals with rheumatic diseases. With prolonged engagement in the exercise protocol and subsequent mesocycles, even greater benefits could potentially be achieved.

3.6 – Conclusion

This study highlights the benefits and the feasibility of an adapted physical exercise protocol in individuals with rheumatic diseases. The results from the first mesocycle showed significant improvements in strength, flexibility, and pain management. Although there are also indications of improvements in aerobic capacity and quality of life, these results remain unclear with the first analysis.

While the study showed good outcomes, several limitations were identified. The most significant were the short duration of the study and the small number of participants. Additional limitations included variability in testing operators, reliance on self-reported data in questionnaires, and the absence of a standardized protocol, which restricted broader comparisons across a larger number of subjects. Addressing these limitations could strengthen the reliability of findings in further applications.

With further exposure to subsequent mesocycles, with progressively increasing intensity and volume, it is expected that participants could achieve even greater improvements in strength, endurance, and overall functionality. Additionally, implementing a standardized protocol for a larger group of participants could provide more robust insights into the generalizability of these results.

In conclusion, this study proves the essential role of individualized and adapted physical exercise programs in managing rheumatic diseases. Beyond the physical benefits, the significant reduction in pain underlines the importance of exercise as an integral component of therapeutic strategies for these conditions.

4. BIBLIOGRAFY

[1] Watts RA, Conaghan PG, Denton C, Foster H, Isaacs J, Müller-Ladner U. Oxford textbook of rheumatology (4th ed.); *Oxford University Press.* 2013*;* 839–897.

[2] Alamanos Y, Voulgari PV, Drosos AA**.** Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum.* 2006; 36: 182–188.

[3] Firestein GS. Evolving concepts of rheumatoid arthritis. *Nature.* 2003; 423: 356–361.

[4] McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol.* 2007; 7: 429–442.

[5] Muller-Ladner U, Ospelt C, Gay S, Distler O, Pap T. Cells of the synovium in rheumatoid arthritis. Synovial fibroblasts. *Arthritis Res Ther.* 2007; 9:223.

[6] Walsh NC, Crotti TN, Goldring SR, Gravallese EM. Rheumatic diseases: the effects of inflammation on bone. *Immunol Rev.* 2005; 208: 228–251.

[7] van Baarsen LG, Wijbrandts CA, Timmer TC et al. Synovial tissue heterogeneity in rheumatoid arthritis in relation to disease activity and biomarkers in peripheral blood. *Arthritis Rheum.* 2010; 62: 1602–1607.

[8] Gerlag DM, Raza K, van Baarsen LG et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. *Ann Rheum Dis.* 2012; 71: 638–641.

[9] MacGregor AJ, Snieder H, Rigby AS et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum*. 2000; 43: 30–37.

[10] Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum.* 1987; 30: 1205–1213.

[11] van der Helm-van Mil AH, Huizinga TW, Schreuder GM et al. An independent role of protective HLA class II alleles in rheumatoid arthritis severity and susceptibility. *Arthritis Rheum.* 2005; 52: 2637–2644.

[12] Makrygiannakis D, Hermansson M, Ulfgren AK et al. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. *Ann Rheum Dis.* 2008; 67: 1488–1492.

[13] Scott IC, Steer S, Lewis CM, Cope AP. Precipitating and perpetuating factors of rheumatoid arthritis immunopathology: linking the triad of genetic predisposition, environmental risk factors and autoimmunity to disease pathogenesis. *Best Pract Res Clin Rheumatol.* 2011; 25: 447–468.

[14] Wu HJ, Ivanov, II, Darce J et al. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. *Immunity.* 2010; 32: 815–827.

[15] Scher JU, Abramson SB. The microbiome and rheumatoid arthritis. *Nat Rev Rheumatol*. 2011; 7: 569–578.

[16] Fleming A, Crown JM, Corbett M. Early rheumatoid disease. I. Onset. *Ann Rheum Dis.* 1976; 35: 357–360.

[17] Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. *Ann Rheum Dis.* 2006; 65: 845 –851.

[18] Nishimura K, Sugiyama D, Kogata Y et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med.* 2007; 146: 797–808.

[19] van Leeuwen MA, van Rijswijk MH, van der Heijde DM et al. The acute phase response in relation to radiographic progression in early rheumatoid arthritis: a prospective study during the first three years of the disease. *Br J Rheumatol.* 1993; 32 Suppl 3: 9–13.

[20] Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 1988; 31: 315–324.

[21] Silman AJ, Symmons DP. Selection of study population in the development of rheumatic disease criteria: comment on the article by the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum.* 1995; 38: 722–723.

[22] van der Heijde D, van der Helm-van Mil AH, Aletaha D et al. EULAR definition of erosive disease in light of the 2010 ACR/EULAR rheumatoid arthritis classification criteria. *Ann Rheum Dis.* 2013; 72: 479–481.

[23] Suurmeijer TP, Waltz M, Moum T et al. Quality of life profiles in the first years of rheumatoid arthritis: results from the EURIDISS longitudinal study. *Arthritis Rheum.* 2001; 45: 111–121

[24] Hakkinen A, Arkela-Kautiainen M, Sokka T, Hannonen P, Kautiainen H. Self-report functioning according to the ICF model in elderly patients with rheumatoid arthritis and in population controls using the multidimensional health assessment questionnaire. *J Rheumatol.* 2009; 36: 246–253

[25] Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extraarticular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis.* 2003; 62: 722–727.

[26] Raven RW, Weber FP, Price LW. The necrobiotic nodules of rheumatoid arthritis; case in which the scalp, abdominal wall, involving striped muscle, larynx, pericardium, involving myocardium, pleurae, involving lungs, and peritoneum were affected. *Ann Rheum Dis.* 1948; 7: 63–75.

[27] McGavin DD, Williamson J, Forrester JV et al. Episcleritis and scleritis. A study of their clinical manifestations and association with rheumatoid arthritis. *Br J Ophthalmol.* 1976; 60: 192–226.

[28] Saag KG, Kolluri S, Koehnke RK et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. *Arthritis Rheum.* 1996; 39: 1711–1719.

[29] National Institute of Health and Clinical Excellence. *Clinical Guideline 79. Rheumatoid Arthritis. National Guideline for management and treatment in adults.* National Collaborating Centre for Chronic Conditions, Royal College of Physicians, London, 2009. Available at: http://guidance.nice.org.uk/CG79/Guidance/pdf/English.

[30] Scottish Intercollegiate Guidelines Network. *Management of early rheumatoid arthritis: A national clinical guideline*. Available at: www.sign.ac.uk/guidelines/fulltext/123/index.html.

[31] Luqmani R, Hennell S, Estrach C, et al. British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the Management of Rheumatoid Arthritis (the first 2 years). *Rheumatology.* 2006; 45: 1167–1169.

[32] Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs. *Ann Rheum Dis.* 2010; 69: 964–975;

[33] Salliott C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis.* 2009; 68: 1100–1104.

[34] Braun J, Kästner P, Flaxenberg P et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum.* 2008; 58: 73–81.

[35] Spies CM, Bijlsma JW, Burmester GR, Buttgereit F. Pharmacology of glucocorticoids in rheumatoid arthritis. *Curr Opin Pharmacol*. 2010; 10: 302–307.

[36] Kirwan JR, Bijlsma JWJ, Boers M, Shea B. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane Database Syst Rev.* 2007; 1: CD006356.

[37] Dougados M, Baeten D. Spondyloarthritis. *Lancet.* 2011; 377 (9783: 2127‑2137). *Dis* 2011; (70: 25‑31.)

[38] Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int.* 2003; 23: 61–66.

[39] Rudwaleit M, Haibel H, Baraliakos X et al. The early disease stage in axial spondylarthritis: Results from the German spondyloarthritis inception cohort. *Arthritis Rheum.* 2009; 60: 717–727.

[40] Khan MA. HLA B27 and its subtypes in world populations. *Curr Opin Rheumatol.* 1995; 7: 263–269.

[41] Reveille JD, Hirsch R, Dillon CF, Carroll MD, Weisman MH. The prevalence of HLA B27 in the United States: Data from the U.S. National Health and Nutrition Examination Survey, 2009. *Arthritis Rheum.* 2011.

[42] Saraux A, Guillemin F, Guggenbuhl P et al. Prevalence of spondyloarthropathies in France: 2001. *Ann Rheum Dis.* 2005; 64: 1431–1435.

[43] Helmick CG, Felson DT, Lawrence RC et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* 2008; 58: 15–25.

[44] Adomaviciute D, Pileckyte M, Baranauskaite A et al. Prevalence survey of rheumatoid arthritis and spondyloarthropathy in Lithuania. *Scand J Rheumatol.* 2008; 37: 113–119.

[45] van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984; 27: 361–368.

[46] Rudwaleit M, van der Heijde D, Landewe R et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis.* 2009; 68: 777–783.

[47] Rudwaleit M, Jurik A, Hermann KG et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis.* 2009; 68: 1520–1527

[48] Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum.* 2005; 52: 1000–1008.

[49] van den Berg R, de Hooge M, Rudwaleit M et al. ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. *Ann Rheum Dis.* 2012.

[50] Sieper J, Rudwaleit M, Baraliakos X et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* 2009; 68 Suppl 2: ii1–ii44.

[51] Poddubnyy D, Rudwaleit M, Haibel H et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann Rheum Dis.* 2011; 70: 1369–1374.

[52] Brandt HC, Spiller I, Song IH et al. Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis. *Ann Rheum Dis.* 2007; 66: 1479–1484.

[53] Braun A, Saracbasi E, Grifk a J, Schnitker J, Braun J. Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain? *Ann Rheum Dis.* 2011; 70: 1782–1787.

[54] Hermann J, Giessauf H, Schaffler G, Ofner P, Graninger W. Early spondyloarthritis: usefulness of clinical screening. *Rheumatology (Oxford)*. 2009; 48: 812–816.

[55] Braun J, Sieper J. Ankylosing spondylitis. *Lancet.* 2007; 369: 1379–1390.

[56] Garrett S, Jenkinson T, Kennedy LG et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol.* 1994; 21: 2286–2291.

[57] Calin A, Garrett S, Whitelock H et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol.* 1994; 21: 2281–2285.

[58] Lukas C, Landewe R, Sieper J et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2009; 68: 18–24.

[59] Machado P, Landewe R, Lie E, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis.* 2010; 70: 47–53.

[60] Landewe R, Dougados M, Mielants H, van der Tempel H, van der Heijde D. Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. *Ann Rheum Dis.* 2009; 68: 863–867.

[61] Baraliakos X, Listing J, Rudwaleit M et al. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. *Ann Rheum Dis.* 2007; 66: 910–915.

[62] Poddubnyy D, Haibel H, Listing J et al. Baseline radiographic damage, elevated acute phase reactants and cigarette smoking status predict radiographic progression in the spine in early axial spondyloarthritis. *Arthritis Rheum.* 2012; 64: 1388–1398.

[63] Rudwaleit M, Feldtkeller E, Sieper J. Easy assessment of axial spondyloarthritis (early ankylosing spondylitis) at the bedside. *Ann Rheum Dis.* 2006; 65: 1251–1252.

[64] Rudwaleit M, van der Heijde D, Landewe R et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis.* 2011; 70: 25–31.

[65] Zeboulon N, Dougados M, Gossec L. Prevalence and characteristics of uveitis in the spondyloarthropathies: a systematic literature review. *Ann Rheum Dis.* 2008; 67: 955–959.

[66] Sieper J, Klopsch T, Richter M et al. Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomized, double-blind, controlled study. *Ann Rheum Dis.* 2008; 67: 323–329.

[67] van der Heijde D, Baraf HS, Ramos-Remus C et al. Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two week, randomized, controlled study. *Arthritis Rheum.* 2005; 52: 1205–1215.

[68] Braun J, van den Berg R, Baraliakos X et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis.* 2011; 70: 896–904.

[69] Helliwell PS, Wright V. Psoriatic arthritis: clinical features. In: Klippel JH, Dieppe PA. (eds) *Rheumatology*. Mosby, London, 1998:6.21.1–6.21.8.

[70] Helliwell PS, Wright V. Seronegative spondarthritides. In: Anderson JAD (ed) Clinical rheumatology international practice and research: epidemiological, sociological and environmental aspects of rheumatology. *Balliere.* Tindall, London. 1987; 491–524.

[71] Moll JMH, Wright V. Psoriatic arthritis. *Semin Arthrits Rheum.* 1973; 3: 51–78.

[72] Taylor WJ, Gladman DD, Helliwell PS, Marchesoni A, Mease PJ, Mielants H. Classification criteria for psoriatic arthritis. *Arthritis & Rheumatism.* 2006; 54: 2665–2673.

[73] FitzGerald O, Dougados M. Psoriatic arthritis: one or more diseases? *Best Pract Res Clin Rheumatol.* 2006; 20: 435–450.

[74] Harrison BJ, Silman AJ, Barrett EM, Scott DG, Symmons DP. Presence of psoriasis does not influence the presentation or short-term outcome of patients with early inflammatory polyarthritis. *J Rheumatol.* 1997; 24: 1744–1749.

[75] Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: a systematic review. *J Rheumatol.* 2008; 35: 1354–1358.

[76] Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Time trends in epidemiology and characteristics of psoriatic arthritis over 3 decades: a population-based study. *J Rheumatol.* 2009; 36: 361–367.

[77] Qureshi A, Dominguez P, Duffin K et al. Psoriatic arthritis screening tools. *J Rheum.* 2008; 35: 1423–1425.

[78] Reich K, Kruger K, Mossner R, Augustin M. Epidemiology and clinical pattern of psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of 1511 patients with plaque-type psoriasis. *Br J Dermatol.* 2009; 160: 1040–1047.

[79] Di Angelo S, Mennillo G, Cutro M et al. Sensitivity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. *J Rheumatol.* 2009; 36: 368–370.

[80] Coates L, Conaghan P, Emery P et al. Sensitivity and specificity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. *Arthritis Rheum.* 2012; 64: 3150–3155.

[81] Chandran V, Schentag CT, Gladman DD. Sensitivity and specificity of the CASPAR criteria for psoriatic arthritis in a family medicine clinic setting. *J Rheumatol.* 2010; 35: 2069–2070.

[82] Jones SM, Armas JB, Cohen MG et al. Psoriatic arthritis: outcome of disease subsets and relationship of joint disease to nail and skin disease. *Br J Rheumatol.* 1994; 33: 834–839.

[83] Gladman DD, Farewell VT, Nadeau C. Clinical indicators of progression in psoriatic arthritis: multivariate relative risk model. *J Rheumatol.* 22: 675–679, 1995.

[84] Rothschild BM, Pingitore C, Eaton M. Dactylitis: implications for clinical practice. *Semin Arthritis Rheum* 1998; 28: 41–47.

[85] Gorter S, van der Heijde DMFM, van der Linden S et al. Psoriatic arthritis: performance of rheumatologists in daily practice. *Ann Rheum Dis.* 2002; 61: 219–224.

[86] Hyslop E, McInnes IM, Woodburn J, Turner D. Foot problems in psoriatic arthritis: high burden and low care provision. *Ann Rheum Dis.* 2010; 69: 928.

[87] Vasey FB, Deitz C, Fenske NA, Germain BF, Espinoza LR. Possible involvement of Group A streptococci in the pathogenesis of psoriatic arthritis. *J Rheumatol.* 1982; 9: 719–722.

[88] Eder L, Law T, Chandran V et al. Association between environmental factors and onset of psoriatic arthritis in patients with psoriasis. *Arthritis Care Res.* 2011; 63: 1091–1097.

[89] Scarpa R, Del Puente A, di Girolamo C et al. Interplay between environmental factors, articular involvement, and HLA-B27 in patients with psoriatic arthritis. *Ann Rheum Dis.* 1992; 51: 78–79.

[90] Julkunen H, Rajanen JA, Kataja J. Severe trauma as an aetiological factor in rheumatoid arthritis. *Scand J Rheum.* 1974; 3: 97–102.

[91] Gladman DD, Farewell VT, Pellett F, Schentag C, Rahman P. HLA is a candidate region for psoriatic arthritis. evidence for excessive HLA sharing in sibling pairs. *Hum Immunol.* 2003; 64: 887–889.

[92] Nograles KE, Brasington RD, Bowcock AM. New insights into the pathogenesis and genetics of psoriatic arthritis. *Nat Clin Pract Rheumatol.* 2009; 5: 83–91.

[93] Queiro-Silva R, Torre-Alonso JC, Tinture-Eguren T, Lopez-Lagunas I. The effect of HLA-DR antigens on the susceptibility to, and clinical expression of psoriatic arthritis. *Scand J Rheumatol.* 2004; 33: 318–322.

[94] Korendowych E, Dixey J, Cox B, Jones S, McHugh N. The influence of the HLA-DRB1 rheumatoid arthritis shared epitope on the clinical characteristics and radiological outcome of psoriatic arthritis. *J Rheumatol.* 2003; 30: 96–101.

[95] Liu Y, Helms C, Liao W et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet.* 2008; 4: e1000041.

[96] Ritchlin CT, Kavanaugh A, Gladman DD et al. Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis.* 2009; 68: 1387–1394.

[97] Gossec L, Smolen JS, Gaujoux-Viala C et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis.* 2012; 71: 4–12.

[98] Cuellar ML, Citera G, Espinoza LR. Treatment of psoriatic arthritis. *Baillieres Clin Rheumatol* 1994; 8: 483–498.

[99] Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. *J Rheumatol.* 2006; 33: 1422–1430.

[100] Heiberg MS, Kaufmann C, Rodevand E et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6-month results from a longitudinal, observational, multicentre study. *Ann Rheum Dis.* 2007; 66: 1038–1042.

[101] Kingsley G, Kowalczyk A, Taylor H et al. Methotrexate is not disease modifying in psoriatic arthritis: the MIPA trial. *Arthritis Rheum.* 2010; 62 (Suppl 10): 664.

[102] Fraser AD, van Kuijk AW, Westhovens R et al. A randomized, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann Rheum Dis.* 2005; 64: 859–864.

[103] Menon T, Wroblewski BM. Charnley low friction arthroplasty in patients with psoriasis. *Clin Orthop.* 1983; 248: 108–111

[104] Majno G, Joris I. Cells, Tissues and Disease (Oxford Univ. Press, 2004; Kumar, V., Cotran, R. S. & Robbins, S. L. *Robbins Basic Pathology*. Saunders, 2003.

[105] Medzhitov R. Origin and physiological roles of inflammation. *Nature.* 2008; 454, 428–435.

[106] Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med.* 1999*;* 340:115–126.

[107] Petersen AM, Pedersen, BK. The anti-inflammatory effect of exercise. *J. Appl. Physiol.* 2005; 98, 1154–1162.

[108] Flynn MG, McFarlin BK. Toll-like receptor 4: link to the anti-inflammatory effects of exercise? *Exerc. Sport Sci. Rev.* 2006; 34, 176–181.

[109] Gleeson M, McFarlin BK, Flynn MG. Exercise and Toll-like receptors. *Exerc. Immunol. Rev.* 2006*;* 12, 34–53.

[110] Kawanishi N, Yano H, Yokogawa Y, Suzuki K. Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophages in high-fat-diet-induced obese mice. *Exerc. Immunol. Rev.* 2010; 16, 105–118.

[111] Timmerman KL, Flynn MG, Coen PM, Markofski MM, Pence BD. Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? *Leukoc. Biol.* 2008; 84, 1271–1278.

[112] Yeh S-H, Chuang H, Lin LW, Hsiao C-Y, Eng HL. Regular tai chi chuan exercise enhances functional mobility and CD4CD25 regulatory T cells. *Br. J. Sports Med.* 2006; 40, 239–243.

[113] Wang J, et al. Effect of exercise training intensity on murine T-regulatory cells and vaccination response. *Scand. J. Med. Sci. Sports.* 2011.

[114] Akira S, Taga T, and Kishimoto T. Interleukin-6 in biology and medicine. *Adv Immunol.* 1993; 54: 1–78.

[115] Dinarello CA. The role of the interleukin-1-receptor antagonist in blocking inflammation mediated by interleukin-1. *N Engl J Med.* 2000; 343: 732–734.

[116] Tilg H, Dinarello CA, Mier JW. IL-6 and APPs: anti-inflammatory and immunosuppressive mediators. *Immunol Today.* 1997; 18: 428–432.

[117] Febbraio MA, Pedersen BK. Muscle-derived interleukin-6: mechanisms for activation and possible biological roles. *FASEB J.* 2002; 16: 1335–1347.

[118] Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration and adaptation. *Physiol Rev.* 2000; 80: 1055–1081.

[119] Pedersen BK, Steensberg A, Schjerling P. Muscle-derived interleukin-6: possible biological effects. *J Physiol.* 2001; 536: 329–337.

[120] Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. *Exerc Immunol Rev.* 2002; 8: 6–48.

[121] Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Proand anti-inflammatory cytokine balance in strenuous exercise in humans. *J Physiol.* 1999; 515: 287–291.

[122] Ostrowski K, Schjerling P, Pedersen BK. Physical activity and plasma interleukin-6 in humans—effect of intensity of exercise. *Eur J Appl Physiol.* 2000; 83: 512–515.

[123] Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, Febbraio M, Saltin B. Searching for the exercise factor: is IL-6 a candidate. *J Muscle Res Cell Motil.* 2003; 24: 113–119.

[124] Keller C, Steensberg A, Pilegaard H, Osada T, Saltin B, Pedersen BK, Neufer PD. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. *FASEB J.* 2001; 15: 2748–2750.

[125] Hiscock N, Chan MH, Bisucci T, Darby IA, Febbraio MA. Skeletal myocytes are a source of interleukin-6 mRNA expression and protein release during contraction: evidence of fiber type specificity. *FASEB J.* 2004; 18: 992–994.

[126] Penkowa M, Keller C, Keller P, Jauffred S, Pedersen BK. Immunohistochemical detection of interleukin-6 in human skeletal muscle fibers following exercise. *FASEB J.* 2003; 17: 2166–2168.

[127] Steensberg A, Keller C, Starkie RL, Osada T, Febbraio MA, Pedersen BK. IL-6 and TNF-α expression in, and release from, contracting human skeletal muscle. *Am J Physiol Endocrinol Metab.* 2002; 283: E1272–E1278.

[128] Steensberg A, van Hall G, Osada T, Sacchetti M, Saltin B, Klarlund PB. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. *J Physiol.* 2000; 529: 237–242.

[129] Pedersen M, Steensberg A, Keller C, Osada T, Zacho M, Saltin B, Febbraio MA, Pedersen BK. Does the aging skeletal muscle maintain its endocrine function? *Exerc Immunol Rev.* 2004; 10: 42–55.

[130] Schindler R, Mancilla J, Endres S, Ghorbani R, Clark SC, Dinarello CA. Correlations and interactions in the production of interleukin- 6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. *Blood.* 1990; 75: 40–47.

[131] Matthys P, Mitera T, Heremans H, Van Damme J, Billiau A. Anti-gamma interferon and anti-interleukin-6 antibodies affect staphylococcal enterotoxin B-induced weight loss, hypoglycemia, and cytokine release in D-galactosamine-sensitized and unsensitized mice. *Infect Immun.* 1995*;* 63: 1158–1164.

[132] Mizuhara H, O'Neill E, Seki N, Ogawa T, Kusunoki C, Otsuka K, Satoh S, Niwa M, Senoh H, Fujiwara H. T cell activation associated hepatic injury: mediation by tumor necrosis factors and protection by interleukin 6. *J Exp Med.* 1994; 179: 1529–1537.

[133] Steensberg A, Fischer CP, Keller C, Moller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab.* 2003; 285: E433–E437.

[134] Moore KW, O'Garra A, de Waal MR, Vieira P, Mosmann TR. Interleukin-10. *Annu Rev Immunol.* 1993; 11: 165–190.

[135] Pretolani M. Interleukin-10: an anti-inflammatory cytokine with therapeutic potential. *Clin Exp Allergy.* 1999; 29: 1164–1171.

[136] Wang P, Wu P, Anthes JC, Siegel MI, Egan RW, Billah MM. Interleukin-10 inhibits interleukin-8 production in human neutrophils. *Blood.* 1994; 83: 2678–2683.

[137] Wang P, Wu P, Siegel MI, Egan RW, Billah MM. IL-10 inhibits transcription of cytokine genes in human peripheral blood mononuclear cells. *J Immunol.* 1994; 153: 811–816.

[138] Dinarello CA. The role of the interleukin-1-receptor antagonist in blocking inflammation mediated by interleukin-1. *N Engl J Med.* 2000; 343: 732–734.

[139] Pue CA, Mortensen RF, Marsh CB, Pope HA, Wewers MD. Acute phase levels of C-reactive protein enhance IL-1 beta and IL-1ra production by human blood monocytes but inhibit IL-1 beta and IL-1ra production by alveolar macrophages. *J Immunol.* 1996; 156: 1594–1600.

[140] Hernández-Hernández MV, Díaz-González F. Role of physical activity in the management and assessment of rheumatoid arthritis patients. *Reumatol Clin*. 2017; 13(4):214-220.

[141] Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, Nightingale P, Kitas GD, Koutedakis Y. Individualized aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. *Ann Rheum Dis,* 2013; 72, 1819–1825.

[142] Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA.* 2009; 30: 2024–2035.

[143] de Jong Z, Munneke M, Kroon HM, van Schaardenburg D, Dijkmans BA, Hazes JM, et al. Long-term follow-up of a high-intensity exercise program in patients with rheumatoid arthritis. *Clin Rheumatol.* 2009; 28: 663–671.

[144] de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. *Arthritis Rheum.* 2003; 48: 2415–2424.

[145] Lee P, Kennedy AC, Anderson J, Buchanan WW. Benefits of hospitalization in rheumatoid arthritis. *Q J Med*. 1974; 43: 205–214.

[146] Feinberg J, Brandt KD. Use of resting splints by patients with rheumatoid arthritis. *Am J Occup Ther.* 1981; 35: 173–178.

[147] Plasqui G. The role of physical activity in rheumatoid arthritis. *Physiol Behav.* 2008; 94: 270–275.

[148] van den Ende CH, Breedveld FC, le Cessie S, Dijkmans BA, de Mug AW, Hazes JM. Effect of intensive exercise on patients with active rheumatoid arthritis: a randomized clinical trial. *Ann Rheum Dis.* 2000; 59: 615–621.

[149] Sandberg ME, Wedren S, Klareskog L, Lundberg IE, Opava CH, Alfredsson L, et al. Patients with regular physical activity before onset of rheumatoid arthritis present with milder disease. *Ann Rheum Dis.* 2014; 73: 1541–1544.

[150] Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation*. 2003; 107: 1303–1307.

[151] Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Panoulas VF, Douglas KM, Jamurtas AZ, et al. What predicts obesity in patients with rheumatoid arthritis? An investigation of the interactions between lifestyle and inflammation. *Int J Obes (Lond).* 2010; 34: 295–301.

[152] Elkan AC, Hakansson N, Frostegard J, Hafstrom I. Low level of physical activity in women with rheumatoid arthritis is associated with cardiovascular risk factors but not with body fat mass: a cross-sectional study. *BMC Musculoskelet Disord*. 2011; 12: 13.

[153] Hernandez-Hernandez V, Ferraz-Amaro I, Diaz-Gonzalez F. Influence of disease activity on the physical activity of rheumatoid arthritis patients. *Rheumatology (Oxford).* 2014; 53: 722–731.

[154] Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, Wilson M, Nevill AM, Koutedakis Y, et al. Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. *Eur J Cardiovasc Prev Rehabil.* 2009; 16: 188–194.

[155] Baillet A, Zeboulon N, Gossec L, Combescure C, Bodin LA, Juvin R, et al. Efficacy of cardiorespiratory aerobic exercise in rheumatoid arthritis: meta-analysis of randomized controlled trials. *Arthritis Care Res (Hoboken).* 2010; 62:984–992.

[156] Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database Syst Rev.* 2009; CD006853.

[157] van den Ende CH, Vliet Vlieland TP, Munneke M, Hazes JM. Dynamic exercise therapy for rheumatoid arthritis. *Cochrane Database Syst Rev.* 2000; CD000322.

[158] El Kabbaj S, Rkain H, Benslama I, Lakhdar T, Znat F, Benbrahim L, et al. Physical activity and rheumatoid arthritis: results from quest-RA Moroccan study. *Ann Rheum Dis.* 2013; 72.

[159] Ertek S, Cicero A. Impact of physical activity on inflammation: effects on cardiovascular disease risk and other inflammatory conditions. *Arch Med Sci.* 2012; 8: 794–804.

[160] Hakkinen A, Sokka T, Kotaniemi A, Hannonen P. A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. *Arthritis Rheum.* 2001; 44: 515–522.

[161] Sjoquist ES, Brodin N, Lampa J, Jensen I, Opava CH. Physical activity coaching of patients with rheumatoid arthritis in everyday practice: a long-term follow-up. *Musculoskeletal Care.* 2011; 9: 75–85.

[162] Jahanbin I, Hoseini Moghadam M, Nazarinia MA, Ghodsbin F, Bagheri Z, Ashraf AR. The effect of conditioning exercise on the health status and pain in patients with rheumatoid arthritis: a randomized controlled clinical trial. *Int J Community Based Nurs Midwifery.* 2014; 2: 169–176.

[163] Baillet A, Payraud E, Niderprim VA, Nissen MJ, Allenet B, François P, et al. A dynamic exercise programme to improve patients' disability in rheumatoid arthritis: a prospective randomized controlled trial. *Rheumatology (Oxford).* 2009; 48: 410–415.

[164] Ibanez J, Izquierdo M, Martinez-Labari C, Ortega F, Grijalba A, Forja L, et al. Resistance training improves cardiovascular risk factors in obese women despite a significative decrease in serum adiponectin levels. *Obesity (Silver Spring).* 2010; 1 8: 535–541.

[165] Baillet A, Vaillant M, Guinot M, Juvin R, Gaudin P. Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. *Rheumatology (Oxford).* 2012; 51: 519–527.

[166] Hakkinen A, Sokka T, Hannonen P. A home-based two-year strength training period in early rheumatoid arthritis led to good long-term compliance: a five-year follow-up. *Arthritis Rheum*. 2004; 51: 56–62.

[167] Hakkinen A, Hakkinen K, Hannonen P. Effects of strength training on neuromuscular function and disease activity in patients with recent-onset inflammatory arthritis. *Scand J Rheumatol.* 1994; 23: 237–242.

[168] Stenstrom CH, Arge B, Sundbom A. Dynamic training versus relaxation training as home exercise for patients with inflammatory rheumatic diseases. A randomized controlled study. *Scand J Rheumatol.* 1996; 25: 28–33.

[169] Lemmey AB, Williams SL, Marcora SM, Jones J, Maddison PJ. Are the benefits of a high-intensity progressive resistance training program sustained in rheumatoid arthritis patients? A 3-year follow-up study. *Arthritis Care Res (Hoboken).* 2012; 64: 71–75.

[170] Melikoglu MA, Karatay S, Senel K, Akcay F. Association between dynamic exercise therapy and IGF-1 and IGFBP-3 concentrations in the patients with rheumatoid arthritis. *Rheumatol Int.* 2006; 26: 309–313.

[171] Neuberger GB, Aaronson LS, Gajewski B, Embretson SE, Cagle PE, Loudon JK, et al. Predictors of exercise and effects of exercise on symptoms, function, aerobic fitness, and disease outcomes of rheumatoid arthritis. *Arthritis Rheum.* 2007; 57: 943–952.

[172] Stenstrom CH, Minor MA. Evidence for the benefit of aerobic and strengthening exercise in rheumatoid arthritis. *Arthritis Rheum.* 2003; 49: 428–434.

[173] Rausch Osthoff AK, Niedermann K, Braun J, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Ann Rheum Dis*. 2018; 77(9): 1251–1260.

[174] Pécourneau V, Degboé Y, Barnetche T, Cantagrel A, Constantin A, Ruyssen-Witrand A. Effectiveness of Exercise Programs in Ankylosing Spondylitis: A Meta-Analysis of Randomized Controlled Trials. *Arch Phys Med Rehabil*. 2018; 99(2): 383–389.

[175] Sveaas SH, Berg IJ, Provan SA, et al. Effectiveness of high intensity exercise on disease activity and cardiovascular risk in active axial spondyloarthritis: a randomized controlled pilot study. *PLoS One.* 2014; 9: e108688.

[176] Masiero S, Bonaldo L, Pigatto M, Lo Nigro A, Ramonda R, Punzi L. Rehabilitation treatment in patients with ankylosing spondylitis stabilized with tumor necrosis factor inhibitor therapy: a randomized controlled trial. *J Rheumatol.* 2011; 38: 1335–1342.

[177] Altan L, Korkmaz N, Dizdar M, Yurtkuran M. Effect of Pilates training on people with ankylosing spondylitis. *Rheumatol Int*. 2012; 32: 2093–2099.

[178] Durmus D, Alayli G, Cil E, Canturk F. Effects of a home-based exercise program on quality of life, fatigue, and depression in patients with ankylosing spondylitis. *Rheumatol Int.* 2009; 29: 673–677.

[179] Durmus D, Alayli G, Uzun O, et al. Effects of two exercise interventions on pulmonary functions in the patients with ankylosing spondylitis. *Joint Bone Spine.* 2009; 76: 150–155.

[180] Kjeken I, Bo I, Ronningen A, et al. A three-week multidisciplinary in-patient rehabilitation programme had positive long-term effects in patients with ankylosing spondylitis: randomized controlled trial. *J Rehabil Med.* 2013; 45: 260–267.

[181] Ferna´ndez-de-Las-Pen˜as C, Alonso-Blanco C, Alguacil-Diego IM, Miangolarra-Page JC. One-year follow-up of two exercise interventions for the management of patients with ankylosing spondylitis. *Am J Phys Med Rehabil.* 2006; 85: 559–567.

[182] Leung FP, Yung LM, Laher I, Yao X, Chen ZY, Huang Y. Exercise, vascular wall and cardiovascular diseases: an update (Part 1). *Sports Med.* 2008; 38: 1009–1024.

[183] Peters MJ, van Eijk IC, Smulders YM, et al. Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis. *J Rheumatol.* 2010; 37: 161-166.

[184] Singh HJ, Nimarpreet K, Ashima, Das S, Kumar A, Prakash S. Study of bone mineral density in patients with ankylosing spondylitis. *J Clin Diagn Res.* 2013; 7: 2832–2835.

[185] Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev.* 2011; (7): CD000333.

[186] Aytekin E, Caglar NS, Ozgonenel L, Tutun S, Demiryontar DY, Demir SE. Home-based exercise therapy in patients with ankylosing spondylitis: effects on pain, mobility, disease activity, quality of life, and respiratory functions. *Clin Rheumatol.* 2012; 31: 91–97.

[187] Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis.* 2010; 69: 325–331.

[188] Ogdie A, Yu Y, Haynes K, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis.* 2015; 74: 326–332.

[189] Wenger NK. Prevention of cardiovascular disease: highlights for the clinician of the 2013 American College of Cardiology/American Heart Association guidelines. *Clin Cardiol*. 2014; 37: 239–251.

[190] Klingberg E, Lorentzon M, Mellstrom D, et al. Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. *Arthritis Res Ther.* 2012; 14: R108.

[191] Borer KT. Physical activity in the prevention and amelioration of osteoporosis in women: interaction of mechanical, hormonal and dietary factors. *Sports Med.* 2005; 35: 779–830.

[192] Feltelius N, Hedenstrom H, Hillerdal G, Hallgren R. Pulmonary involvement in ankylosing spondylitis. *Ann Rheum Dis.* 1986; 45: 736–40.

[193] Viitanen JV, Suni J, Kautiainen H, Liimatainen M, Takala H. Effect of physiotherapy on spinal mobility in ankylosing spondylitis. *Scand J Rheumatol.* 1992; 21: 38–41.

[194] Wei M, Kampert JB, Barlow CE, et al. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA.* 1999; 282: 1547–1553.

[195] Karapolat H, Eyigor S, Zoghi M, Akkoc Y, Kirazli Y, Keser G. Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study. *Eur J Phys Rehabil Med*. 2009; 45: 449–457.

[196] Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* 2007; 39: 1423–1434.

[197] Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011; 43: 1334–1359.

[198] Jennings F, Oliveira HA, de Souza MC, Cruz Vda G, Natour J. Effects of aerobic training in patients with ankylosing spondylitis. *J Rheumatol.* 2015; 42: 2347–2353.

[199] Silva EM, Andrade SC, Vilar MJ. Evaluation of the effects of global postural reeducation in patients with ankylosing spondylitis. *Rheumatol Int.* 2012; 32: 2155–63.

[200] Kessler J, Chouk M, Ruban T, Prati C, Wendling D, Verhoeven F. Psoriatic arthritis and physical activity: a systematic review. *Clin Rheumatol*. 2021; 40: 4379–4389.

[201] Thomsen RS, Nilsen TIL, Haugeberg G, Bye A, Kavanaugh A, Hoff M. Effect of high-intensity interval training on cardiovascular disease risk factors and body composition in psoriatic arthritis: a randomised controlled trial. RMD Open. 2018;4:e000729.

[202] Kviatkovsky MJ, Ramiro S, Landewé R, Dougados M, Tubach F, Bellamy N, et al. The minimum clinically important improvement and patient-acceptable symptom state in the BASDAI and BASFI for patients with ankylosing spondylitis. *J Rheumatol.* 2016; 43: 1680–1686.

[203] Khanna D, Pope J, Khanna PP, Maloney M, Samedi N, Norrie D, et al. The minimally important difference for the fatigue visual analog scale in patients with rheumatoid arthritis followed in an academic clinical practice. *J Rheumatol.* 2008; 35: 2339–2343.

[204] Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. *Ann Emerg Med.* 1996; 27: 485–489.

[205] Frankel HC, Han J, Li T, Qureshi AA. The association between physical activity and the risk of incident psoriasis. *Arch Dermatol.* 2012; 148: 918–924.

[206] Balato N, Megna M, Palmisano F, Patruno C, Napolitano M, Scalvenzi M, Ayala F. Psoriasis and sport: a new ally? *J Eur Acad Dermatol Venereol.* 2015; 29: 515–520.

[207] Thomsen RS, Nilsen TIL, Haugeberg G, Gulati AM, Kavanaugh A, Hoff M. Adiposity and physical activity as risk factors for developing psoriatic arthritis: longitudinal data from a population-based study in Norway. *Arthritis Care Res.* 2019; 73: 432–441.

[208] Wervers K, Herrings I, Luime JJ, Tchetverikov I, Gerards AH, Hazes JMW, Vis M. Association of physical activity and medication with enthesitis on ultrasound in psoriatic arthritis. *J Rheumatol.* 2019; 46: 1290–1294.

[209] Kehl AS, Corr M, Weisman MH. Enthesitis. *Arthritis Rheumatol (Hoboken NJ).* 2016; 68: 312–322.

[210] Lorenzin M, Ortolan A, de Hooge M, Frallonardo P, Piccoli A, Cozzi F, et al. Lengthening the time intervals between doses of biological agents in psoriatic arthritis patients: A single-center retrospective study. *Int J Immunopathol Pharmacol SAGE Publications Ltd*. 2015; 28: 479–87.

[211] Fong W, Holroyd C, Davidson B, Armstrong R, Harvey N, Dennison E, et al. The effectiveness of a real-life dose reduction strategy for tumour necrosis factor inhibitors in ankylosing spondylitis and psoriatic arthritis. *Rheumatology.* 2016; 55: 1837–1842.

[212] Coates LC, Soriano ER, Corp N, Bertheussen H, Callis Duffin K, Campanholo CB, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol.* 2022; 18: 465–479.

[213] Henaux S, Ruyssen-Witrand A, Cantagrel A, Barnetche T, Fautrel B, Filippi N, et al. Risk of losing remission, low disease activity or radiographic progression in case of bDMARD discontinuation or tapering in rheumatoid arthritis: systematic analysis of the literature and meta-analysis. *Ann Rheum Dis BMJ Publishing Group Ltd*. 2018; 77: 515–22.

[214] Verhoef LM, van den Bemt BJ, van der Maas A, Vriezekolk JE, Hulscher ME, van den Hoogen FH, et al. Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane Database Syst Rev*. 2019; 5: CD010455.

[215] Webers C, Nikiphorou E, Boonen A, Ramiro S. Tapering or discontinuation of biological disease-modifying antirheumatic drugs in axial spondyloarthritis: A review of the literature and discussion on current practice. *Joint Bone Spine*. 2023; 90: 105482.

[216] Cantini F, Niccoli L, Cassarà E, Kaloudi O, Nannini C. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study. *Biol Targets Ther.* 2013; 7: 1–6.

[217] Brandt J, Khariouzov A, Listing J, Haibel H, Sörensen H, Grassnickel L, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum.* 2003; 48: 1667–1675.

[218] Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis.* 2020; 79: 700–712.

[219] Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis BMJ Publishing Group Ltd.* 2020; 79: 685–699.

[220] Smolen JS, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis.* 2018; 77: 3–17.

[221] Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis.* 2011; 70: 47–53.

[222] Studenic P, Aletaha D, de Wit M, Stamm TA, Alasti F, Lacaille D, et al. American College of Rheumatology/EULAR Remission Criteria for Rheumatoid Arthritis: 2022 Revision. Arthritis Rheumatol Hoboken NJ 2023; 75: 15–22.

[223] Wasserman K. Principles of exercise testing and interpretation. *Meas Dur Integr Cardiopulm Exerc test.* 1999; Available from: http://ci.nii.ac.jp/naid/10018658535/en/

[224] Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine parameters of aerobic function during exercise. *J Appl Physiol Respir Environ Exerc Physiol*. 1981; 50: 217–221.

[225] American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing [published correction appears in Am J Respir Crit Care Med. 2003 May 15;1451-2]. *Am J Respir Crit Care Med*. 2003; 167: 211–277.

[226] Luks AM, Glenny RW, Robertson HT. Introduction to Cardiopulmonary Exercise Testing. *New York, NY: Springer New York.* 2013. Available from: http://link.springer.com/10.1007/978-1-4614-6283-5

[227] Ross RM, Beck KC, Casaburi R, Johnson BD, Marciniuk DD, Wagner PD, et al. ATS/ACCP Statement on Cardiopulmonary Exercise Testing (multiple letters). *Am J Respir Crit Care Med.* 2003; 167: 1451.

[228] Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010; 122: 191–225.

[229] Grassi F, Negrini D, Porro CA. Fisiologia umana. *Poletto Editore*. 2015; 885-888

[230] Janicki JS, Sheriff DD, Robotham JL, Wise RA. Cardiac output during exercise: contributions of the cardiac, circulatory, and respiratory systems. *Compr Physiol.* 2010; 649–704.

[231] Arena R, Arrowood JA, Fei DY, Helm S, Kraft KA. Maximal aerobic capacity and the oxygen uptake efficiency slope as predictors of large artery stiffness in apparently healthy subjects. *J Cardiopulm Rehabil Prev*. 2009; 29: 248–254.

[232] Weisman IM, Zeballos RJ. *Clinical Exercise Testing. European Respiratory Society* ©; 2002; 339.

[233] Rikli RE, Jones CJ. Functional fitness normative scores for community-residing older adults, ages 60-94. *J Aging Phys Act.* 1999; 7: 162–181.

[234] Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Ex Sport*. 1999; 70: 113–119.

[235] Różańska-Kirschke A, Kocur P, Wilk M, Dylewicz P. The Fullerton Fitness Test as an index of fitness in the elderly. *Medical Rehabilitation.* 2006; 10: 9–16.

[236] Welch SA, Ward RE, Beauchamp MK, Leveille SG, Travison T, Bean JF. The Short Physical Performance Battery (SPPB): A Quick and Useful Tool for Fall Risk Stratification Among Older Primary Care Patients. *J Am Med Dir Assoc.* 2021; 22: 1646–1651.

[237] Sole G, Hamren J, Milosavljevic S, Nicholson H, Sullivan SJ. Test-retest reliability of isokinetic knee extension and flexion. *Arch Phys Med Rehabil*. 2007; 88: 626–31

[238] Spruit MA, Sillen MJ, Groenen MT, Wouters EF, Franssen FM. New normative values for handgrip strength: results from the UK Biobank. J *Am Med Dir Assoc.* 2013; 14: 775.e5–11.

[239] Gajdosik RL, Bohannon RW. Clinical measurement of range of motion. Review of goniometry emphasizing reliability and validity. *Phys Ther*. 1987; 67: 1867–1872.

[240] Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. *Int J Behav Nutr Phys Act*. 2011; 8: 115.

[241] Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992; 305: 160–164.

WEB REFERENCES

http://guidance.nice.org.uk/TA199 - National Institute for Health and Care Excellence (NICE): Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis.