



Universiteit
Leiden
The Netherlands

Implementation of physical activity recommendations in people with axial spondyloarthritis

Rausch Osthoff, A.K.

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General introduction

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Rheumatic and Musculoskeletal Diseases (RMDs) encompass over 200 conditions of the musculoskeletal system, including osteoarthritis and inflammatory arthritis. RMDs are characterized by pain, stiffness, loss of locomotor function and, sometimes, premature death (1). About one quarter of the European population of all ages is affected by RMDs. This results in direct and indirect healthcare costs of around EUR 240 billion per year, or some 2% of the gross domestic product of European countries (2). Physical Activity (PA) is one of the most important lifestyle factors influencing human health, along with balanced diet, cessation of smoking and/or abusive substance use, and reduction of stress. PA is considered a modifiable behaviour that can reduce the risk of developing an RMD, positively influence its course and prevent some of its consequences (3-6). This thesis will in part focus on axial spondyloarthritis, a form of inflammatory arthritis.

Definition, consequences, and epidemiology of axial spondyloarthritis

Axial spondyloarthritis (axSpA), which includes both radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA), is a chronic, inflammatory RMD that predominately affects the sacroiliac joints and spine. Approximately 30% of people with axSpA have both axial and peripheral joint involvement (7). AxSpA can also present with associated musculoskeletal (e.g., arthritis, enthesitis, dactylitis) or extra-articular manifestations (e.g., uveitis, inflammatory bowel disease, cardiovascular diseases) (8, 9). In people with axSpA, the presence of disease characteristics based on the Assessment of Spondyloarthritis international Society (ASAS) classification varies significantly. These variations include, for example, radiographic or non-radiographic changes (10), or the presence of biomarkers such as the C-reactive protein, the human leukocyte antigen (HLA) B27 status, or the erythrocyte sedimentation rate (11). The chronic inflammation of the axial skeleton leads to back pain and progressive stiffness. The symptoms can be improved with exercise, but not through inactivity. The chronic inflammation may also result in functional and structural impairments (8), e.g., reduced flexibility (12), balance (13), muscle strength (14), or cardio-respiratory capacity (15). Comorbidities are common in people with axSpA. According to data from an international ASAS comorbidity study including 3'370 patients (66% male, mean $\pm$ SD age 43 $\pm$ 14 years), 51% of people with axSpA suffered from at least one comorbidity and 9% from three or more comorbidities (16). This study also showed that the higher the number of comorbidities (reflected by a higher score on the Rheumatic Disease Comorbidity Index (17)), the greater the impact on physical function, work ability, and quality of life (16). In Spanish, German and Dutch cohorts, the comorbidities most commonly found were hypertension, depression and obesity (18-20). It has also been demonstrated that people with axSpA have an increased risk of cardiovascular diseases (21).

The prevalence of axSpA in the general population is about 0.1%-0.6%, according to European disease prevalence data (22, 23). The male-female prevalence ratio is equal (24).

However, there are gender differences regarding radiologic prognosis (with males more affected) and burden of disease (with females more affected) (25). Characteristically, disease onset is in early adulthood and results in considerable personal burden of disease and negative economic consequences for the individual and society (26-29). Despite efforts in clinical practice to increase awareness and improve diagnostic procedures, the diagnostic delay is still 2-11 years on average, with women waiting longer than men (30-32).

The management of axSpA

The recommendations of the European Alliance of Associations for Rheumatology (EULAR) for the management of axSpA define the aim of primary treatment as: 'To maximise long-term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation' (8). This treat-to-target strategy (goal of remission or low disease activity) implies that the management of axSpA should be personalised, and a combination of pharmacological and non-pharmacological treatment modalities applied (8, 9, 33). The recommended first-line pharmacological treatment for people suffering from pain and stiffness is the prescription of nonsteroidal anti-inflammatory drugs (NSAIDs). For people with consistently high disease activity, additional biological therapies are available (8). Two groups of biological disease-modifying antirheumatic drugs (bDMARDs) and their biosimilars (drugs that are virtually identical to the original) have been approved as effective and safe: tumour necrosis factor inhibitors (TNFi) and interleukin17A inhibitors (IL17Ai) (34). The bDMARDs are used to achieve a threshold of remission or low disease activity and focus on physical function (35). The maximal reduction of symptoms by pharmacological treatment enhances the success of non-pharmacological treatment (36). The ASAS recommendations for non-pharmacological treatment include physiotherapy, education, smoking cessation, and the promotion of PA (8).

Regarding the reduction of disease activity in the management of axSpA, there is evidence to show that combining pharmacological and non-pharmacological treatment modalities through the combination of bDMARDs and physiotherapy is superior to medication alone (36-38). The effect on disease activity was established using the Bath Ankylosing Spondylitis Mobility Index (BASMI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores (37, 38).

In research specifically on the effectiveness of exercise programmes, routine pharmacological therapy was usually continued in both the intervention and the control groups. In the most recent Cochrane review from 2019, 14 randomized controlled trials investigating the effect of exercise programmes were examined. The exercise programmes had a mean duration of 12 weeks at a median frequency of three sessions per week and consisted mainly of land-based flexibility, breathing and strength exercises, in combination with standard-NSAIDs or

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DMARDs (39). The conclusions drawn from the pooled data were that these programmes slightly improve function, potentially reduce pain and, probably, slightly reduce disease activity (moderate-to-low quality evidence) in comparison with no intervention (but standard-NSAIDs) (39). The authors were uncertain about potential adverse events due to lack of evidence and insufficient reporting in the studies (39). The effectiveness of physiotherapy interventions is difficult to demonstrate because of methodological weaknesses, such as small sample sizes, heterogeneous study populations, insufficient description of the interventions and/or flaws in the assessments (39).

The studies investigated in the Cochrane review (39) represent the traditional exercise concept for people with axSpA that is commonly employed in current clinical practice. However, it has been suggested that this traditional exercise concept is no longer state-of-the-art. Recent studies, for example from Sveaas and colleagues (40), have shown that high-intensity aerobic exercise interventions have promising effects on disease activity, inflammatory markers, and symptoms such as pain, fatigue, and stiffness. A greater focus on aerobic exercises also seems to be advisable because of the growing body of knowledge on the increased cardiovascular risk in this patient group (41, 42). Patients also appear to support such a shift in the focus of axSpA exercises and concur with the inclusion of fitness-related exercises alongside to conventional disease-specific exercises (43).

Definition of physical activity and recommendations

Physical Activity (PA) is defined as ‘any bodily movement produced by skeletal muscles that results in energy expenditure above resting (basal) levels’ (44, 45). PA encompasses any exercise, sport or physical activities done as part of daily living, occupation, leisure and active transportation (46). *Exercise* is a subcategory of PA that is ‘planned, structured, and repetitive and [that] has as a final or intermediate objective to improve or maintain one or more dimensions of physical fitness’ (44). In contrast, *therapeutic exercises and exercise therapy* comprise specific exercises designed to address distinct functional health problems and are supervised by a qualified health professional, e.g., a physiotherapist.

The World Health Organisation (WHO) provides current, evidence-based public health PA recommendations on the amount (frequency, intensity, and duration) and type of regular PA necessary to offer significant health benefits and mitigate health risks. The *current PA recommendations* for adults (including elderly or people with chronic conditions) encompass four exercise dimensions: cardiorespiratory/aerobic; muscle strength; flexibility; and neuromotor exercises (3, 47). A person is advised to perform at least 150-300 minutes of moderate-intensity PA, or 75-150 minutes of vigorous-intensity aerobic PA (or combination of these) per week, plus additional muscle strengthening activities involving the major muscle groups on at least two days of the week (47). Flexibility and neuromotor exercises are additionally recommended on three or more days during the week (3, 47). Correspondingly,

sitting time should be reduced to a minimum (47).

The intensity of PA is defined through the estimation of energy demands of the metabolic system, i.e., metabolic equivalent of task (MET) (48): for example, walking at 5km/h is described by 3.2METs and classified as a moderate-intensity aerobic activity; and jogging at 9km/h is described by 8.8METs and classified as vigorous aerobic activity. The use of absolute measures may be misleading, however, because personal factors, such as weight, sex, age, and fitness level are not considered (46). For this reason, a relative *measure of intensity* (e.g., %MET_{max}, %HR_{max} or perceived exertion), which measures the energy costs relative to the individual's maximal capacity, is more appropriate. Moderate exercise is defined as 64% - 76% of the maximum heart rate (%HR_{max}) and vigorous exercise as 77% - 95%HR_{max}. Another commonly used assessment to evaluate the intensity of exercise is the Borg Rating of Perceived Exertion Scale, which measures the individual's effort and exertion, breathlessness, and fatigue during PA (49). On a numeric visual scale of 6-20, the numbers 6- 12 indicate a moderate-intensity exercise and the numbers 13-20 a vigorous-intensity exercise (49).

The dose-response relationship between daily PA and health benefits has been confirmed (50). Exceeding the minimum recommended amount of PA improves fitness, reduces the risk factors of chronic conditions, and prevents unhealthy weight gain (46). Furthermore, there is evidence that shorter vigorous-intensity exercise (e.g., 30 minutes of activity $\geq$ 6METs) is better than longer moderate-intensity exercise (e.g., 60 minutes of activity at 3-6METs) and is associated with a greater reduction of cardiovascular risk (51) and lower mortality rate in the general population (52).

People not meeting the minimum recommendations are considered physically inactive. The WHO stresses that, when possible, people with chronic conditions should try to meet the public health PA recommendations. It also states that exercising below the recommended levels may still be beneficial to people not able or willing to fulfil the recommended amount of PA (47). The American College of Sports Medicine (ACSM) supports this statement, providing evidence on the importance of PA in the prevention and treatment of chronic conditions. It provides examples of appropriate PA programmes and guidance for the performance of exercise (3).

Physical activity and axSpA

Meeting the PA recommendations described above and incorporating the four exercise dimensions of aerobic, muscle strength, flexibility and neuromotor exercising is especially difficult for people with axSpA. They face barriers of pain, fatigue, or stiffness that healthy people do not have (53). Other aspects, such as the fear of flare-ups or the presence of comorbidities, may also hamper participation in certain types of exercise. Some physical

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consequences of the disease, such as osteoporosis (risk of fracture), severe deformities of the spine (risk of neurological complication), or extra-articular manifestations (e.g., tendons, bowels, kidney, eyes), can make an active lifestyle even more difficult to realise (54). It is therefore not surprising that people living with axSpA have been found to be generally less physically active than healthy controls (55-57). Expert support from physicians and health professionals in rheumatology (HPRs), e.g., physiotherapists, may thus be required to identify and address the individual challenges with respect to PA behaviour.

Exercise is medicine for people with axSpA: clear recommendations are needed

Despite the fact that exercise (and group exercise, in particular) is mentioned in the recommendations and guidelines for the management of axSpA (8, 58), it has been uncertain for some time whether the public health PA recommendations are applicable to people with axSpA. The public health PA recommendations focus on aerobic exercises at an appropriate dosage (moderate/vigorous intensity, and most days per week frequency) which contrasts with the content of most exercise programmes for people with axSpA found in the literature (39, 47). This is an important distinction.

In 2016, this highly relevant issue led to the initiation of an EULAR task force on the development of PA recommendations for people with RMDs, including axSpA (among others).

The first part of this thesis concerns the development process of the EULAR PA recommendations for people with RMDs, while the second part describes the lessons learned from their pilot implementation specifically in people with axSpA.

Implementation of PA recommendations in people with axSpA

After the development of a clinical innovation, it must subsequently be translated and implemented into clinical routine. Implementation is the uptake of research findings by routine health care in the clinical, organisational and policy contexts using strategies tailored to the target population, setting, and goals for improvement (59). However, the implementation of innovations into clinical routine is a great challenge (60, 61). It needs a planned, systematic approach with clear strategies. Successful implementation must be based on an analysis of the contextual factors and the knowledge-practice gap, inclusion of stakeholders, and theory-informed systematic approach (59, 62). The Grol&Wensings' model of change (63) is a theoretical approach that is commonly applied to guide and describe an implementation process. After a comprehensive analysis of current practice

and targets of change, implementation strategies and interventions can be developed, evaluated, and continuously and cyclically adapted (63).

It is known that awareness of the public health PA recommendations and their resulting benefits does not necessarily lead to behavioural changes (64-66). PA is behaviourally complex and increasing PA as a lifestyle change remains a challenge (67, 68). A successful health behaviour change can be defined as ‘the shift from risky behaviours to the initiation and maintenance of healthy behaviours and functional activities, and the self-management of chronic health conditions’ (69). Several theories have been proposed to explain PA behaviour, which is determined by individual, social, environmental, and societal factors (68). Common to many theories is the central distinction of motivation, which is conceptualised (for example) in intention, stage of change, and autonomous motivation (70). Motivation determines whether an individual will change PA behaviour over the long term. Consequently, an understanding of how PA promotion interventions can influence motivation is critical. The use of behaviour change techniques (71), such as goal-setting and self-monitoring, has been shown to be associated with beneficial changes in PA behaviour (70, 72). Fenton and colleagues (73) summarised the evidence on theory-informed interventions for people with axSpA. They emphasised that motivation and theories should be used more intensively to develop interventions and learn “how things work”. This would help to develop new strategies, optimise current interventions, and support the translation of the theory into practice process.

Physical activity promotion in people with axSpA in Switzerland

In Switzerland, 76% of the adult population is considered physically active (74). The Swiss health care system is fee-for-service and regulated by law and organised at cantonal level (75, 76). The cost of only a few PA promotion intervention programmes for people with chronic conditions is partly refunded by health insurance (77). A Swiss national agency for the development of guidelines does not exist and evidence-based interventions are often not systematically applied in clinical care (78). The Swiss Association for Rheumatology did not publish its own guidelines for the management of axSpA, but referenced those published by EULAR and the American College of Rheumatology.

The Ankylosing Spondylitis Association of Switzerland (Schweizerische Vereinigung Morbus Bechterew, SVMB, www.bechterew.ch) represents approximately 4'300 members with axSpA. The SVMB is connected to the national association Swiss League Against Rheumatism and is a member of the Ankylosing Spondylitis International Federation (ASIF) and the European Alliance of Associations for Rheumatology Patient Representatives (EULAR PARE). Since the early 1980s, the SVMB offers - among other services - physiotherapist-supervised, weekly exercise group therapy in approximately 65 locations

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across Switzerland. The concept of this exercise group therapy was, however, outdated since it was mainly based on flexibility and low-intensity strength exercising. Recent evidence indicates that greater attention should be paid to cardiovascular exercise (79-82), individual dosage of exercise intensity based on regular assessments (72, 83-85), encouragement to use exercise for self-management of disease and regular performance of individual exercise (86). Consequently, in line with the ambition of the EULAR task force, the SVMB aimed to translate the EULAR PA recommendations into a new exercise group concept that would meet both disease-specific exercising and general PA recommendations, and to subsequently implement it into routine clinical care.

Outline of this thesis

Given the lack of specific PA recommendations for people with RMDs, particularly axSpA, and their deficient implementation into clinical care, the aims of this thesis were to:

- 1) Describe the development, definition, and evidence base of the 2018 EULAR recommendations for PA in people with inflammatory arthritis and osteoarthritis.
- 2) Evaluate the pilot implementation of exercising according to the EULAR PA recommendations in exercise groups for people with axSpA in Switzerland, including the analysis of the situation, determinants of PA behaviour, and the exploration of a muscle strength assessment.

The first aim is addressed in the following chapters:

- Chapter 2 describes the development and definition of the 2018 EULAR recommendations for PA in people with inflammatory arthritis and osteoarthritis.
- Chapter 3 summarises the evidence on the effects of exercise and PA promotion, according to public health recommendations, in people with rheumatoid arthritis, spondyloarthritis, and hip/knee osteoarthritis. This meta-analysis informed the EULAR task force, defining the EULAR recommendations for PA.

The second aim is addressed in the following chapters:

- Chapter 4 evaluates patients' use of physiotherapy and their perspective on it. A quantitative analysis of the current situation in the Netherlands and Switzerland.
- Chapter 5 explores the patients' beliefs related to PA. A qualitative evaluation of the current situation in Switzerland.
- Chapter 6 describes the reliability of an adapted core strength endurance test battery. This assessment is needed to tailor individual exercises. It is a relevant component of the implementation strategy described below.
- Chapter 7 elucidates the implementation strategy and lessons learned from the pilot implementation of the PA recommendations in axSpA exercise group therapy in Switzerland.
- Chapter 8 discusses the most important findings of the studies in this thesis

and their implications for clinical care. Suggestions for further research are also presented.

- Chapter 9 summarises the thesis.

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