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Reduced appendicular lean body mass, muscle strength and size of type 2 muscle fibers in spondyloarthritis vs. healthy controls: A cross-sectional study.

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Abstract

Objective: The effect of chronic, systemic inflammation on muscle tissue is largely unknown. The purpose of this study was to investigate body composition, muscle function and muscle morphology in patients with spondyloarthritis (SpA).

Methods: Ten male SpA patients (mean ±SD age 39 ±4.1 years) were compared with ten healthy controls matched for age, body mass index and self-reported level of exercise. Body composition was measured by dual energy X-ray absorptiometry. Quadriceps femoris (QF) strength was assessed by maximal isometric contractions prior to test of muscular endurance. Magnetic resonance imaging of QF was used to calculate specific muscle strength. Percutaneous needle biopsy samples were taken from *m. vastus lateralis.*

Results: SpA patients presented with significantly lower appendicular lean body mass (LBM) (p= 0.02), but there was no difference in bone mineral density, fat mass or total LBM. Absolute and specific strength of the left QF was significantly lower in SpA patients (p= 0.01 and 0.04) with a parallel trend observed for the right leg. Biopsy samples from the SpA patients revealed significantly smaller cross-sectional area (CSA) of type 2 muscle fibers (p= 0.04), but no difference in CSA type 1 fibers.

Conclusion: Results indicate that the presence of SpA disease is associated with reduced appendicular LBM, muscle strength and type 2 fiber CSA. Further research is needed to investigate whether catabolic pathways are up-regulated in SpA patients. Strength training may be an effective countermeasure against these negative effects on muscle indicated in SpA patients.

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Acronyms:

AS- Ankylosing Spondylitis
BASDAI – Bath Ankylosing Spondylitis disease activity index
BASFI – Bath Ankylosing Spondylitis functional index
BASMI – Bath Ankylosing Spondylitis metrology index
BMD – Bone mineral density
BMI – Body mass index
BM – Body mass
CAT - Catalase
CSA – Cross-sectional area
COX – Cytochrome C oxidase
CVD – Cardiovascular disease
DXA - Dual energy X-ray absorptiometry
FFMI – Fat free mass index
FM – Fat mass
FoxO – Forkhead box O
GPX - Glutathione peroxidase
IGF-1 – Insulin-like growth factor 1
IHC- Immunohistochemistry
IL-1 – Interleukin 1
IL-6 – Interleukin 6
IL-17- Interleukin 17
IL-22 – Interleukin 22
IL-23 – Interleukin 23
LBM – Lean body mass
MGF – Mechano growth factor
MHC – Myosin heavy chain
NSAIDs – Non-Steroidal Anti-Inflammatory Drugs
OA - Osteoarthritis
QF – Mm. Quadriceps Femoris
RA – Rheumatoid Arthritis
ROS – Reactive Oxygen Species
SpA – Spondyloarthritis
SOD- Superoxide dismutase
SR – Sarcoplasmatic reticulum
TNF – Tumor necrosis factor

1. Introduction

The previous decades have provided insight regarding the important role of physical activity and physical fitness in prevention and treatment of a wide range of diseases (Wen et al., 2011). Global recommendations issued by the World Health Organization promote habitual physical activity for all age groups, stating that the health benefits outweigh potential harms (WHO, 2014). Recent studies have linked sedentary time to increased risk of various diseases and shown an inverse correlation between physical activity and lifestyle disease (Grontved & Hu, 2011; Sattelmair et al., 2011). The benefits of exercise may reduce the burden of disease and curtail the use of health services and possibly also the need for pharmacological treatment. For some patient groups, regular physical activity can possibly lead to a more benign disease course and reduce social costs.

The Norwegian Directorate of Health recommend that all adults engage in resistance exercise at least twice a week (Helsedirektoratet, 2014). For healthy individuals, physiological adaptations to various subtypes of resistance training are well established and the benefits of regular resistance training are many (ACSM, 2009; Wernbom, Augustsson, & Thomee, 2007). It is however unclear whether we can directly translate the resistance exercise recommendations for healthy adults to include patients with a chronic, inflammatory disease. The effect of chronic, systemic inflammatory disease on skeletal muscle tissue is largely unknown. Consequently, exploring whether there are pathological changes in muscle tissue in patients with spondyloarthritis (SpA) can provide useful insight. Furthermore, such knowledge may have implications in how we prescribe resistance training for this patient group.

1.1 Aim

The aim of this study was to compare body composition, muscle function and muscle morphology in SpA patients to healthy controls. Results of the study may provide insight into whether there are differences between SpA patients and controls concerning the items listed above. The results may generate future hypotheses concerning whether we can assume that patients with SpA will adapt to strength training in the same manner as the general population, or if we may need to modify resistance exercise recommendations to better suit patients with SpA.

1.2 Master thesis

Do male patients with SpA differ in body composition, muscle function or muscle morphology compared to healthy controls?

Null hypothesis: None of body composition, quadriceps femoris (QF) muscle function and QF muscle morphology differ between male patients aged 30-45 with SpA and healthy controls.

Alternative hypothesis: One or more of body composition, QF muscle function or QF muscle morphology differ between male patients aged 30-45 with SpA and healthy controls.

2. Theory

2.1 Spondyloarthritis

SpA is a chronic, inflammatory rheumatic disease. The prevalence estimates to 0.3-0.7 %, with disease onset frequently reported at a young adult age (Haglund et al., 2011; Strand et al., 2013). SpA has been reported to be predominant in males, although some studies show that prevalence among women is higher than what has traditionally been accepted (Lee, Reveille, & Weisman, 2008). The term SpA designates several diseases that share certain clinical and genetic features. Ankylosing Spondylitis (AS) is often viewed as the prototype of SpA as well as the most severe subtype (Ozgocmen & Khan, 2012; Raychaudhuri & Deodhar, 2014) (Ozgocmen & Khan, 2012). This paper will further consider SpA as one disease, but signify different subtypes when appropriate.

SpA symptoms generally precede clinical diagnosis, with an average diagnostic delay of about six years in AS. Typical disease characteristics include inflammatory axial pain, asymmetrical and peripheral oligoarthritis, and enthesopathy. Extra-articular manifestations such as anterior uveitis, psoriasis, and chronic inflammatory bowel disease are also common (Braun & Sieper, 2007; Khan, 2011). Inflammation in SpA may lead to bony erosion and joint destruction, similar to the pathophysiology seen in rheumatoid arthritis (RA). However, in contrast to other rheumatic diseases, axial SpA is also accompanied by axial bone formation in the form of syndesmophytes[1] (Lories & Baeten, 2009).

2.1.1 SpA and physical function

Characteristic clinical features of SpA are axial pain and stiffness, possibly leading to functional impairment (Dougados & Baeten, 2011). Functional loss can be reversible in response to various therapeutic modalities or change in disease activity. However, SpA may also entail irreversible structural changes such as reduced spinal mobility and chest expansion (Landewe, Dougados, Mielants, van der Tempel, & van der Heijde, 2009). This is often a consequence of long-standing disease and is for instance associated with reduced pulmonary function (Berdal, Halvorsen, van der Heijde, Mowe, & Dagfinrud, 2012). However, patient-reported function is reported to be only moderately correlated to radiographic changes (Landewe et al., 2009), indicating that SpA patients may function well despite structural

[1] Syndesmophytes are bony outgrowths from spinal vertebrae

damage. Inflammatory rheumatic disease may also involve serious co-morbidity, and SpA patients have an increased incidence, mortality and morbidity for cardiovascular disease (CVD) compared to the general population (Bremander, Petersson, Bergman, & Englund, 2011; Mathieu, Gossec, Dougados, & Soubrier, 2011; Papagoras, Voulgari, & Drosos, 2013). Researchers are still attempting to discern the horse's mouth of SpA and increased risk of CVD. Studies have shown alterations of traditional CVD risk factors in patients with SpA, with systemic inflammation also recognized as an independent risk factor for CVD (Ridker, Wilson, & Grundy, 2004). SpA patients with high disease activity report less physical activity compared to patients with low disease activity and healthy controls (Fongen, Halvorsen, & Dagfinrud, 2013). In agreement, objective measures of physical activity (PA) reveal lower weekly energy expenditure values as well as scarce levels of vigorous PA in SpA patients matched to healthy controls (Swinnen et al., 2014). Furthermore, the latter study detected no significant correlation between self-reported disease activity and level of PA. Discordantly, equal levels of PA in AS patients and healthy controls were noted when monitored by tri-axial accelerometer, however the sample size was relatively small (n=25 pr. group) (Plasqui et al., 2012). Additionally, Haglund et al. (2012) report a tendency for Swedish SpA patients to fulfill self-reported levels of PA recommendations to a greater extent than the general population, although the results may have been clouded by a responder bias in the SpA population. Regarding cardiorespiratory fitness, a Norwegian study on a large SpA cohort observed significantly lower peak oxygen uptake (VO_{2peak}) in patients vs. controls (Halvorsen et al., 2012) when estimated by an indirect maximal test. Although non-significant, Plasqui et al. (2012) indicate a similar trend (p= 0.09) towards lower physical fitness in AS patients when evaluated by direct measurement of maximal oxygen uptake (VO_{2max}).

In addition to functional disability, SpA patients report impaired health-related quality of life due to domains such as fatigue (Aissaoui et al., 2012), pain (Ozdemir, 2011), activities of daily living (Dagfinrud, Kjeken, Mowinckel, Hagen, & Kvien, 2005) and social participation (Dagfinrud et al., 2005; van Echteld et al., 2006).

2.1.2 Inflammatory pathways in SpA

The etiology and pathogenesis of SpA is unclear although several studies support the notion of a genetic susceptibility. Numerous studies have shown a strong association between the Human Leukocyte Antigen (HLA) B27 and SpA (Ehrenfeld, 2012; McHugh & Bowness, 2012). However, only a small proportion of the 6% of the general population that harbor the

HLA-B27 gene (Reveille & Weisman, 2013) develop SpA, suggesting that additional genes contribute to disease mechanisms in SpA (Ehrenfeld, 2012). Several inflammatory cytokine[2] pathways are implicated in the pathogenesis of SpA. Tumor necrosis factor (TNF) is a cell protein that acts as a pivotal inflammatory agent. In animal models, over-expression of TNF induces systemic inflammation and synovitis. *In vivo* inhibition of TNF in SpA patients effectively reduces disease symptoms. Anti-TNF therapy is however unsuccessful in blocking new bone formation, indicating the presence of additional inflammatory pathways in SpA (reviewed in: Hreggvidsdottir, Noordenbos, & Baeten, 2014; Machado et al., 2013). SpA is genetically associated with genes coding for interleukin 1 (IL-1), a cytokine that may be involved in cartilage and bone destruction. However, IL-1 is also suggested to be upstream to interleukin 17 (IL-17) signaling. There is shortage of human *in vivo* studies linking IL-1 to SpA, and the role of IL-1 in disease pathogenesis remains elusive (Hreggvidsdottir et al., 2014). Interleukin 6 (IL-6) is a pro-inflammatory cytokine that governs acute phase response as measured by CRP (see footnote 16). Even though serum levels of IL-6 are raised in AS patients, these levels are not necessarily correlated to disease activity. In a review article, Hreggvidsdottir et al. (2014) conclude that there is weak evidence from human studies assessing the role of IL-6 as a crucial inflammatory cytokine in SpA. There are however strong indications for an association between SpA and genes coding for the receptor of interleukin 23 (IL-23) (Dougados & Baeten, 2011; Sherlock, Buckley, & Cua, 2014). Overexpression of IL-23 in experimental mice models causes enthesitis and enthesal new bone formation as well as inflammation at the root and valve of the aorta (Sherlock et al., 2012). In human SpA, overexpression of IL-23 is found at both a systemic and local level. Recognized as a pivotal cytokine, IL-23 also regulates production of pro-inflammatory cell signaling molecules interleukin 17 (IL-17) and 22 (IL-22). In SpA, upregulation of IL-17 is associated with recruitment of phagocytic white blood cells to the inflammatory scene, while IL-22 may lead to increased expression of genes governing bone remodeling (Hreggvidsdottir et al., 2014; Sherlock et al., 2014).

2.1.3 Treatment of SpA

Optimal medical treatment combined with supervised and tailored exercise is recognized as the cornerstone treatment of SpA (Braun et al., 2011). A systematic review of non-pharmacological treatment of AS concluded that physical therapy exercises in various

[2] Cytokine: small proteins that are involved in cellular signaling

modalities have positive effects on pain and mobility function (van den Berg, Baraliakos, Braun, & van der Heijde, 2012). Patients present with different courses of disease, and treatment should be tailored to each individual (Braun et al., 2011; Smolen et al., 2014). Pharmacological treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is recommended as the first-line drug treatment for axial pain and stiffness (Dougados & Baeten, 2011). Some individuals with SpA present with a mild disease course that is controlled by on-demand use of NSAIDs, while the majority of patients require continuous medication (Braun & Sieper, 2007; Braun et al., 2011). Over the last decade, the introduction of biological agents directed against TNF has represented a new therapeutic option for SpA patients whom do not respond sufficiently to the use of NSAIDs. TNF blockers target this specific protein and may help to reduce stiffness, pain and swollen joints (Machado et al., 2013). Therapeutic effectiveness of TNF-inhibitors has been enacted in several studies (Baraliakos, van den Berg, Braun, & van der Heijde, 2012), but a Cochrane review emphasizes the need for research on the long-term safety of biological agents (Singh et al., 2011). Anti-TNF therapy is recommended for patients with high disease activity (Braun et al., 2011), but this treatment is not available to all patients due to concurrent or previous disease as well as showing low efficacy in some patients (Dougados & Baeten, 2011).

Disease-modifying anti-rheumatic drugs (DMARDs) are commonly used in inflammatory disease such as RA. The use of these pharmaceuticals such as methotrexate and sulfasalazine have little effect on axial symptoms, and are only recommended in SpA patients who also present with peripheral disease symptoms (Chen, Veras, Liu, & Lin, 2013; Haibel & Specker, 2009).

Exercise has the potential to alleviate disease progress and reduce co-morbidity in patients with SpA. However, an empirical view that intensive exercise can increase disease activity in patients with a chronic, rheumatic disease has previously prevailed (Benatti & Pedersen, 2015; Perandini et al., 2012). Results from studies of other chronic diseases (Pedersen & Saltin, 2006) and a recent randomized control pilot study (Sveaas et al., 2014) imply that a combination of endurance and resistance training can reduce the inflammatory process and possibly modify disease course. Combining both endurance and resistance training is presumably important as various modes of exercise induce different physiological response (Jonas, 2009).

2.1.4 SpA and body composition

Several studies on patients with chronic inflammatory rheumatic diseases have reported an altered body composition in patients with RA. The observed changes in body composition have often been termed rheumatic cachexia (Engvall et al., 2008; Okcu, Yardimci, & Comoglu, 2002; Rall et al., 2002; Roubenoff et al., 1994). Cachexia is defined as *"a complex metabolic syndrome associated with underlying illness and characterized with loss of muscle mass with or without loss of fat mass"* (Evans et al., 2008, p. 794). The diagnostic criteria include weight loss of at least 5% in the last twelve months in concert with three of the following criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass or abnormal biochemistry (Evans et al., 2008; Rolland, Abellan van Kan, Gillette-Guyonnet, & Vellas, 2011). In an attempt to facilitate early detection of cachexia, a consensus paper by Muscaritoli et al. (2010) listed the following diagnostic criteria for detecting pre-cachexia: an underlying chronic disease, unintentional weight loss ≤5% the last six months, chronic or systemic inflammatory response and a reduced desire to eat. Even though some studies report a prevalence of rheumatoid cachexia in a majority of the patients (Engvall et al., 2008; Rall et al., 2002), a study by van Bokhorst et al. (2012) did indeed observe significant alterations in body composition in their patient population, although only 1% of the cohort fit the diagnostic criteria of pre-cachexia or cachexia. The authors further question the relevance of the imperative criteria of involuntary weight loss and anorexia-related symptoms in diagnosing rheumatoid cachexia. In patients with RA, a reduction in lean body mass (LBM) is often accompanied by a maintained or increased fat mass (FM), resulting in a relatively stable body weight (Rajbhandary, Khezri, & Panush, 2011).

Etiology of rheumatoid cachexia is considered to be multi-factorial, and an excessive cytokine production is indicated as one of the underlying mechanisms (Rall & Roubenoff, 2004). The hypothesized catabolic effect of increased circulating levels of inflammatory cell signaling molecules is indicated in a cross-sectional study by Arshad et al. (2007), where loss of fat-free mass was associated with high disease activity. Physical inactivity due to pain and stiffness, resulting in reduced muscle mass and strength, is also implicated as a plausible factor underlying rheumatoid cachexia. Additionally, alterations in hormone level have been suggested as a possible etiological factor. Rall et al. (2002) found no difference in growth hormone (GH) kinetics between RA patients and controls when adjusting for difference in fat mass. Insulin-like growth factor 1 (IGF-1) tended to be lower in RA patients, but this difference was non-significant (p= 0.08). Insulin can inhibit muscle protein degradation, and

an association between reduced peripheral insulin action in inflammatory arthritis and a catabolic milieu, is hypothesized as a potential factor contributing to rheumatoid cachexia (Rall & Roubenoff, 2004; Roubenoff, 2009).

Regarding SpA, there are a few cross-sectional studies comparing body composition in patients to healthy controls. Marcora et al. (2006) observed lower appendicular and total LBM in AS patients, but no difference in FM. These results coincide with the reduced LBM detected in a study with a larger population, although those body composition estimates were predicted by methods of lower validity (Giltay, van Schaardenburg, Gooren, Kostense, & Dijkmans, 1999). Sari et al. (2007) report a lower FM, but no difference in fat free mass index in a male AS population when measured by bioelectrical impedance analysis (BIA) and skinfold thickness. Contrasting these results, Toussirot el al. (2001), Toussirot et al. (2007), Dos Santos et al. (2001) and Plasqui et al. (2012) observed no significant divergence in FM or LBM between AS patients and healthy age- and sex-matched controls. Different methods of measuring body composition are used in the mentioned studies, thus making direct comparisons of results somewhat challenging (Leahy, O'Neill, Sohun, & Jakeman, 2012). Furthermore, study inclusion varies in disease classification criteria. Included study participants also differ in disease duration (range: 8.4±6.3 years to 22±11 years), although self-reported disease activity is somewhat similar (BASDAI range: 3.43±1.82 to 5.2±2.2, not measured in Giltay et al. or dos Santos et al.). In summary, considering the disparate results, the impact of systemic inflammation in SpA on body com remains uncertain. As emphasized by Plasqui et al. (2012), there is a lack of studies concurrently examining body composition and local muscle mass.

Table 1. Studies evaluating body composition in SpA patients.

Author	*Aim of study*	*N (age mean±SD)*	*Measured variables*	*Results*	*Conclusion*	*Comment*
Dos Santos et al. (2001)	Examine regional distribution of bone mass to seek factors leading to bone loss in AS	39 male AS patients (37.6±9.1), 39 controls from a population of military police civilians, age-matched.	Demographic data, CRP, ESR, markers of bone loss, pelvic and thoracolumbar radiographs, DXA, questionnaire on physical activity and calcium intake	Controls significantly heavier (75.6±10.4 kg vs AS 69.3±12.1 kg, $p<0.01$). No significant difference in FM or LBM. Lumbar spine BMD lower in AS (1.085±0.178 vs. 1.232±0.136 g/cm^2, $p<0.01$).	AS is associated with bone loss, but does not affect main variables of BC.	Control group may not be representative to the AS population.
Giltay et al. (1999)	Compare serum levels of CK + other biochemical markers related to skeletal muscle between AS patients and healthy controls	58 AS patients (48, range 28-70), 60 age + sex-matched controls	Demographic data, current use of medication, total energy food intake by food questionnaire, non-fasting blood samples, estimation of LBM by formula validated against BIA	AS: significantly lower serum levels of CK+ other biochemical markers. AS patients decreased LBM (55.8 vs 59.2 kg, p= 0,004). AS: negative correlations between CRP and CK (r=-0.48, $p<0.001$) and aldolase (r=-0.37, p=0.005)	Results suggest decreased circulating markers of skeletal muscles in AS patients	No control for PAL. Estimation of LBM from age, sex and height: limited value, formula may not apply to AS patients (lower height due to kyphosis)
Marcora et al. (2006)	Determine loss of appendicular LBM in AS patients with long disease duration	19 male AS patients, (53±12), 19 age-matched controls	Demographic data including knee height, BASDAI, BASFI, pelvic radiograph, ESR, CRP, PAL questionnaire, DXA, MVC isokinetic knee extension at 60°/sec, grip strength, 30-second sit-to-stand chair test.	12% reduction appendicular LBM (p= 0.005), 11% reduction total LBM (p= 0.002), no difference total BMD, total FM or trunk fat. MVC knee extensor lower in AS (181±67 Nm) vs controls (228±72 Nm, p=0.040). Appendicular LBM correlated with MVC knee (R= 0.79, $p<0.001$)	Preliminary evidence of cachexia in AS patients.	Not matched for PAL – difference in PAL approached sign (p= 0.052), however small biological difference. No measure of diet. *A priori* sample size calculation. Control for sarcopenia by age-matching.
Plasqui et al. (2012)	Compare BC, daily PAL + relationship between BC, serum TNF and PAL	25 patients (48 ±11), 25 healthy controls, age-, sex- and BMI-matched	Demographic data, body water by deuterium dilution, body volume by air-displacement plethymography. PAL: Triaxial accelerometer 7 days. VO2max test. CRP, serum TNF, BASDAI	Height lower in patients (171 vs 177 cm, p=0.01) No difference FM or FFMI, nor accelerometer output. Inverse relationship between CRP and PAL (R= -0.39, $p<0.01$). No correlation between serum TNF and FFMI or BASDAI and LBM.	AS equally healthy to controls. Indicates a need for studies examining muscle mass at a local level.	First study with objective measurement of daily PAL in this patient group. High validity level of measurement techniques. Possible selection bias – recruited patients with moderate to high PAL? No difference in TNF levels between patients and controls could

						imply AS study population does not have severe disease.
Sari et al. (2007)	Evaluate effect of inflammation on insulin resistance, serum leptin levels and BC	28 AS patients (31, range 20-51 yrs), 17 healthy age-matched controls	Demographic data, insulin and leptin levels, ESR, CRP, BASDAI, BASMI, BASFI, BIA, SFT	BIA measures: FM lower in AS men (10.1 %, range 3.8-23.7%) vs controls (18.6 %, range 8.1-24%), $p<0.05$. No difference in FFMI. Serum leptin lower in AS (6.011 vs. 10.924, $p=0.02$)	Inflammation in AS can reduce FM and serum leptin levels	Low serum leptin possibly correlated with low FM. No match for PAL. BIA and SFT are not reference methods for evaluating BC.
Toussirot et al. (2001)	Examine BMD and determine influence of AS on BC	71 AS patients (39.1±11.5), 71 healthy controls, age- and sex-matched.	Demographic data, BASDAI, ESR, CRP, BMD femoral neck, total body DXA, ultrasound right calcaneus	No difference LBM or FM. BMD decreased in AS vs controls at lumbar spine (1.08±0.17 g/cm^2 vs. 1.18±0.13 g/cm^2, $p=0.0002$) and femoral neck (0.97±0.16 g/cm^2 vs. 1.04±0.13 g/cm^2, $p=0.01$)	AS patients decreased BMD at spine and femur, AS disease has no influence on soft tissue.	Did not include patients with criteria of severe disease. No record of medication or PAL. Significant difference in height (AS 169.1 cm vs. controls 172.5 cm, $p= 0.02$)
Toussirot et al. (2007)	Examine adipose tissue in AS patients to evaluate contribution of fat-derived molecules to inflammatory response	53 AS patients, (44.1±0.6), 35 healthy controls, matched for age, sex and PAL questionnaire	Demographic data, BASDAI, BASFI, daily calorie intake, ESR, CRP, total body DXA, serum TNF, ghrelin[3], adiponectin[4], leptin[5], growth hormone, IGF-1[6], IGFBP-3[7]	No sign. difference LBM, FM, IGF-1, growth hormone or level of adiponectin. Leptin decreased in AS (7.6±1.3 ng/mL vs. 10.3±1.5 ng/mL, $p=0.006$). Grehlin increased in AS (1365.5±81.5 pg/mL vs. 1008.2±82.5 pg/mL, $p=0.001$), IGFBP3 decreased in AS (2.6±0.1 µg/mL vs. 3.1±0.1 µg/mL, $p<0.0001$)	AS patients no change in FM. No clear association between adipokines and markers of disease. Decreased IGFBP-3 can inhibit IGF-1 activity and negatively effect LBM..	Match for PAL based on questionnaire estimating VO_{2max}, no assessment of level of strength training. No record of weight or height in demographic data, only BMI. Decreased leptin – a possible mechanism to bar inflammation.

AS: Ankylosing Spondylitis**. BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index. **BASFI**: Bath Ankylosing Spondylitis Functional Index **BASMI:** Bath Ankylosing Spondylitis Metrology Index **BC**: Body Composition **BIA:** Bioelectrical Impedance Analysis. **BMD**: Bone Mineral Density. **BM**: Body Mass. **BMI:** Body Mass Index. **CK:** Creatine Kinase **CRP:** C-reactive protein. **DXA**: Dual energy X-ray absorptiometry **ESR**: Erythrocyte Sedimentation Rate. **FFMI:** Fat Free Mass Index. **FM:** Fat Mass. **LBM:** Lean Body Mass. **MVC:** Maximal voluntary contraction. **PAL**: Physical Activity Level. **SFT:** Skin Fold Thickness. **TNF**: Tumor Necrosis Factor.

[3] Ghrelin is a hormone that induces the release of growth hormone and stimulates appetite (Sato et al., 2012).
[4] Adiponectin is an anti-inflammatory adipokine (adipose-tissue derived cytokine) involved in regulating blood glucose levels and fatty acids breakdown by improving insulin sensitivity (Li, Wang, & Miao, 2011)
[5] Leptin is an adipokine involved in downregulating food intake and enhancing energy expenditure. Levels are highly correlated to FM. May play a pro-inflammatory role in modulating immune response (Otero et al., 2005; Scotece et al., 2014)
[6] IGF – see chapter 1.3.3
[7] IGFBP3 is the main IGF-1 binding protein (Toussirot et al., 2007)

2.1.5 SpA, muscle function and muscle morphology

In addition to joint pain and stiffness, muscle pain and tenderness is a common feature of SpA. The source of muscle pain has been attributed to inflammation in joints and enthesopathy. However, patients with SpA commonly experience considerable relief of pain and stiffness following exercise, possibly indicating a direct involvement of the muscle itself in SpA (G. O. Hopkins, J. McDougall, K. R. Mills, D. A. Isenberg, & A. Ebringer, 1983). Studies have demonstrated reduced muscle strength and increased muscle fatigue in AS patients in a non-active period of disease compared to age- and sex-matched healthy controls (Sahin, Ozcan, Baskent, Karan, Ekmeci, et al., 2011; Sahin, Ozcan, Baskent, Karan, & Kasikcioglu, 2011). In contrast, a small-sample study observed significantly reduced objective physical function, but no difference in quadriceps strength between AS patients and controls (Matschke, Jones, Lemmey, Maddison, & Thom, 2013). Faus-Riera et al. (1991) assessed muscle pathology in 30 patients with AS and 22 controls by means of questionnaire regarding musculoskeletal pain, physical exercises, strength measurements, EMG and biopsy of *mm. quadriceps femoris*, the latter only performed on 24 patients and five controls. They detected mild histological abnormalities in 66.7% of the biopsies yielded from patients, but conclude that the observed morphological changes are a consequence of pain inhibition and reduced activity rather than the inflammatory process. Carrabba et al. (1984) performed a case series study where they found signs of atrophic angulated fibers and a modest prevalence of type 1 fibers in muscles close to the spine in a sample of eight AS patients. Normal histological and histochemical measures in the deltoid muscle was observed in a small subsample of the patients, and the morphological difference in paraspinal muscle was interpreted as being related to axial inflammation. A 30-year old study including 20 AS patients and no controls revealed histological and electromyographic changes in the quadriceps femoris muscle, and indicated a need for further studies concerning the underlying mechanisms (Hopkins, McDougall, Mills, Isenberg, & Ebringer, 1983). The aforementioned studies assessing muscle morphology in SpA are dated, and the disease manifestations in studied patients may differ from what we encounter in our present-day clinical practice due to modern therapeutic options. To our knowledge, there is a paucity of novel studies addressing this topic. However, a study published in 2012 (Beenakker et al.) assessed the influence of chronic systemic inflammation on muscle characteristics in 10 patients with RA, by comparing biopsies from *m. vastus medialis* to biopsies yielded from a population of 27 individuals with osteoarthritis

(OA). They found no significant difference in muscle fiber distribution, level of lipofuscin[8] or ratio of satellite cells, although the latter factor was only studied in a subsample due to limited biomaterial. The authors emphasize that anti-inflammatory medication or low-grade inflammation in OA patients may have tempered the studied variables. Additionally, there are several other histochemical factors known to regulate muscle growth and function that were not included in this study.

In summary, decreased muscle strength in patients with AS may be due to pain, stiffness and inactivity. Inflammation raises stimulation from agents that can cause muscle protein catabolism, thereby potentially affecting muscle mass and loss of strength (Sahin, Ozcan, Baskent, Karan, & Kasikcioglu, 2011). Thus, it seems unclear whether the muscle abnormalities observed in SpA patients are related directly to the underlying inflammation or indirectly through pain, stiffness and reduced levels of physical activity.

2.2 Skeletal muscle

Skeletal muscle is the most abundant tissue in the human body with a primary function of producing movement and maintaining posture, in addition to a role as a metabolic regulator. Muscle mass can vary between individuals due to genetic, physiological and pathologic qualities (Schiaffino, Dyar, Ciciliot, Blaauw, & Sandri, 2013). In a large sample, cross-sectional study that employed whole body magnetic resonance imaging (MRI), skeletal muscle mass was estimated to 38.4% of relative total mass in men, which was significantly higher than the 30.6 % observed in women (Janssen, Heymsfield, Wang, & Ross, 2000). Skeletal muscle mass can be measured by several methods, and Dual energy X-ray absorptiometry (DXA) calculation of LBM corrected for body height has been proposed as a valid indicator of muscle mass (Andreoli, Scalzo, Masala, Tarantino, & Guglielmi, 2009; Toombs, Ducher, Shepherd, & De Souza, 2012). Data from the NHANES[9] study provide DXA-derived body composition reference curves for individuals with an age range of 8-85 years (Kelly, Wilson, & Heymsfield, 2009). Applying to the population included in our study, median reference values for total LBM/height^2 for white males aged 30-45 years are estimated to 18.43-18.78 kg/m^2 when measured with GE Healthcare Lunar DXA systems (Fan et al., 2014).

[8] Lipofuscin is a marker for oxidative damage
[9] National Health and Nutrition Examination Survey: data collected from 1999-2004

2.2.1 Muscle fibers: Structure and function

The smallest functional unit of movement is the motor unit, defined as "an α-motoneuron plus the muscle fibers it innervates" (Lieber, 2010, p. 76). Muscle fibers within one motor unit are of the same phenotype and distributed throughout a region of the muscle. Studies on both animals and humans have shown that slow-contracting motor units are recruited at low levels of voluntary effort. When tension increases, faster motor units are drafted (Lieber, 2010). Skeletal muscle fibers are heterogeneous, and have historically been classified using different schemes. In our study, different muscle fiber types are defined by immunohistochemical properties. This form of fiber-typing scheme uses antibodies that identify what type of myosin heavy chain (MHC) molecule dominates within the different muscle fibers (Lieber, 2010). Bottinelli et al. (1996) divided muscle fibers into five types based on MHC isoforms: type 1 alone, type 1/type 2A, type 2A, type 2A/2X, and type 2X. In terms of physiological function, muscle fibers are often classified as type 1, type 2A and type 2X, with the former often called slow-twitch fibers, and the latter two fast-twitch fibers. Different muscle fiber types appear to generate the same amount of peak isometric tension (Fitts & Widrick, 1996), although a dated study performed on tibialis anterior motor units in cats indicate that fast motor units have the potential of creating slightly more specific tension compared to slow units (Bodine, Roy, Eldred, & Edgerton, 1987). Fibertype distribution is however more consistently correlated with contraction time. Type 2A fibers are considered twice as fast as type 1, while type 2X is 3-4 times as fast as type 1 (Aagaard & Andersen, 1998; Raastad, Paulsen, Refsnes, Rønnestad, & Wisnes, 2010). Since power output is a function of force and velocity, muscles with a predominance of fast-twitch fibers can generate more power compared to muscles with an abundance of slow-twitch fibers. Fibertype distribution differs between various muscle groups as well as among individuals. The latter is exemplified by the observation of a larger volume of type 1 fibers in highly endurance-trained athletes compared to strength athletes (Wilson et al., 2012). Morphological properties of different muscle fiber types pertain to the metabolic differences one can observe between fiber types. Slow-twitch fibers have a larger concentration of oxidative enzymes, a necessity for oxidative phosphorylation. Due to a higher concentration of glycolytic intermediates in the cytoplasm, fast-twitch fibers have a better glycolytic capacity (Lieber, 2010). The number of repetitions achieved at submaximal resistance exercise is considered to partly reflect fiber type distribution (Andersen & Aagaard, 2010). However, a small study (n= 12 male physical education students) by Terzis et al. (2008) observed a non-significant correlation coefficient between fiber composition and

number of leg press repetitions at 70% 1RM and a high correlation (r= 0.70, p= 0.01) between *m. vastus lateralis* capillary density and number of repetitions.

Muscle capillaries are arranged parallel to muscle fibers, and the amount of capillaries reflect the capacity for oxygen delivery from the blood to the muscle cell. Exercise can lead to an increase in maximum oxygen uptake (VO_{2max}) due primarily to changes in maximum cardiac output. At the peripheral level, an exercise-induced rise in capillary density accommodates for elevated blood flow rates by maintaining transit time for each red blood cell within the capillary wall (Bassett & Howley, 2000). Ratio of capillary to muscle fiber can be assessed in muscle biopsies and is proposed to be proportionate to muscle cell mitochondrial volume (Mathieu-Costello & Hepple, 2002). Capillary density is highest in oxidative fibers with 4.2 and 4.0 capillaries per fiber for type 1 and 2A respectively. Type 2X is reported to have a slightly lower capillary density of 3.2 (Egan & Zierath, 2013).

Nestled between myofibrils, mitochondria, often referred to as the cell's powerhouse, are cellular organelles with genetic material (mDNA) independent to cellular DNA. The amount of cellular mitochondria is a balance between mitochondrial synthesis (biogenesis) and mitochondrial degradation (mitophagy) (Russell, Foletta, Snow, & Wadley, 2014). Endurance exercise can increase the number of mitochondria through biogenesis, as well as improve function of the existing mitochondria pool (Yan, Lira, & Greene, 2012). Counterbalance between mitochondrial division (fission) and fusion controls mitophagy, an inherent process in the removal of damaged mitochondria. However, stress conditions may alter the rate of mitophagy. Mitochondrial deficiency can lead to clinical symptoms such as reduced exercise tolerance, fatigue and an advanced production of lactic acid (Hood et al., 2003). In addition to a prime role in synthesizing adenosine triphosphate (ATP) through the electron transport chain, mitochondria can function as signaling platforms for other cellular processes and their action is highly responsive to alterations in cellular morphology and metabolism (McBride, Neuspiel, & Wasiak, 2006). For instance, mitochondria can release factors that are involved in the process of apoptosis[10] (Lanza & Sreekumaran Nair, 2010). The two opposing processes of life-promoting ATP production and cell death rely on a mitochondrial enzyme termed Cytochrome C oxidase (COX). COX transports electrons in the electron transport chain and is pivotal in the production of ATP. To the contrary, cytoplasmic translocation of COX is

[10] Apoptosis is the process of cell death (Lieber, 2010)

associated with increased generation of reactive oxygen species (see chapter 1.3.5) and apoptosis (Huttemann et al., 2011; Y. Li, Park, Deng, & Bai, 2006).

2.2.2 Satellite cells

Myonuclei are incapable of mitosis, and additional nuclei in the muscle fiber are added through recruitment of satellite cells. Also known as myogenic precursor cells, satellite cells are allegedly dormant cells that reside on the surface of the muscle fiber, underneath the basal lamina (Mauro, 1961). Signals for satellite cell activation can be triggered through processes aimed at maintaining muscle fiber homeostasis, in hypertrophic pathways and in regeneration after muscle cell injury. The latter process involves proliferation of satellite cells that evolve into myotubes and further mature to new muscle fibers. In addition to having the ability to breed into a different cell type, satellite cells are also capable of self-renewing by proliferation of daughter cells, hence fitting the description of a stem cell (Kadi et al., 2005; Zammit, Partridge, & Yablonka-Reuveni, 2006).

Volume and function of satellite cells is controlled by several complex intrinsic and extrinsic cellular signaling pathways (Shadrach & Wagers, 2011). A study by Kadi et al. (2004) on 31 young and 27 elderly men and women observed a reduction in the satellite cell pool with increasing age, but no significant gender difference. Relative amount of satellite cells pr. muscle fiber was 6.9% in young men and 7.1% in young women, in contrast to the 3.9% and 4.1% observed in the elderly men and women respectively. The results of the aforementioned study contrasts the non-significant age difference in satellite cell population observed in a study by Roth et al. (2000) on 14 young and 15 elderly individuals. Furthermore, the latter study noted a much lower proportion of satellite cells (1.7-2.8%). Discrepant results can be explained by factors such as divergent levels of physical activity between the study participants, use of different analyzing methods, as well as possible morphological differences between the two muscles (*m. tibialis anterior; m. vastus lateralis)* that were investigated.

Some authors argue that human studies show positive adaptations in satellite cell population in response to exercise, although it is unclear if this response is affected by type of exercise protocol (Kadi et al., 2005). Schiaffino et al. (2013) describe how an acute stimulus, such as an injury or eccentric contractions, can trigger activation and differentiation of satellite cells, thus contributing to muscle fiber growth and regeneration. Contrary to this pathway, exercise

with more moderate loads is suggested to be associated with a growth response resulting from an increased protein synthesis.

2.2.3 Factors that determine muscle fiber size

Myofiber size depends on the sum of myofibrils within the fiber. Myofibrillar hypertrophy is associated with an increase in the number of contractile proteins actin and myosin. In contrast, muscle fiber atrophy is a result of a down-regulation of protein synthesis and an increase in protein degradation. Muscle fiber growth is also aided by addition of cell nuclei through the recruitment of satellite cells, thereby maintaining a hypothesized myonuclear domain ceiling of ~2000 μm^2 (Lieber, 2010; Petrella, Kim, Mayhew, Cross, & Bamman, 2008; Sandri, 2008).

Insulin Growth Factor-1 (IGF-1) is a hormone produced in the liver as well as in target tissues. Autocrine secretion of IGF by muscle cells is assumed following stimuli such as muscle injury or exercise, while paracrine secretion of IGF-1 by macrophages and endothelial cells rapidly increase following damage to myofibers. Endocrine secretion of IGF-1 may also partake, however, studies indicate that the role of circulating IGF-1 in muscle regeneration is modest (reviewed in: Zanou & Gailly, 2013). With a molecular structure similar to insulin, IGF-1 functions as a docking station for signaling enzymes that are involved in catabolic or anabolic muscle pathways (Clemmons, 2009). IGF-1 induces muscle hypertrophy trough the PI-3K/Akt pathway. PI-3K is an enzyme, which when activated triggers recruitment of Akt kinase. This pathway is suggested to separate into several branches that may be involved in hypertrophy signaling, with the activation of mammalian target of rapamycin (mTOR) identified as a significant mediator of protein synthesis. IGF-1 may also incite action through the mitogen-activated protein kinase/extracellular signal-regulated (MAPK/ERK) pathway[11] (Rommel et al., 2001; Schiaffino et al., 2013; Zanou & Gailly, 2013). Factors such as inflammation, disease, malnourishment and various pharmaceuticals may decrease cellular content of IGF-1 mRNA and reduce IGF-1 synthesis (reviewed in: Clemmons, 2009; Schiaffino et al., 2013).

Stimuli from exercise or injury can prompt different splicing of the IGF-1 gene. Translation of one of the mRNA species is hypothesized to mature into a chain of amino acid molecules that deviates from the mature IGF-1 protein. This IGF-1Ec (IGF-1Eb in rodents) isoform has been

[11] Primary response of MAPK activation is growth, remodeling, transcription (Powers, Ji, Kavazis, & Jackson, 2011)

labeled mechano-growth factor (MGF) (Dai, Wu, Yeung, & Li, 2010). Based on *in vitro* studies on C2C12[12] mouse cells, up-regulation of MGF is indicated in playing a role in satellite cell proliferation and activation. Levels of MGF subside while levels of IGF-1 increase in the differentiation phase of muscle cell regeneration or growth, suggesting that MGF opposes muscle cell differentiation (Yang & Goldspink, 2002). These results concur with the observation of enriched levels of satellite cells following the addition of MGF to human primary muscle cell cultures derived from healthy and diseased subjects (Ates et al., 2007). Attempting to examine MGF-signaling *in vivo*, Philippou et al. (2009) detected a quick and transient increase in MGF, accompanied by an extended rise in IGF-1 following eccentric exercise. However, as reviewed by Matheny et al. (2010), levels of MGF are shown to be comparable to or even lower than IGF-1 in early phases of proliferation, thus one cannot dismiss the possibility that MGF poses as a confounding factor.

Atrophy is associated with a decrease in muscle fiber size due to a loss of organelles, cytoplasm and protein content. Accelerated protein degradation is mainly a result of increased activity in a multi-enzymatic process known as the ubiquitin-proteasome pathway (Mitch & Goldberg, 1996; Sacheck, Ohtsuka, McLary, & Goldberg, 2004; Schiaffino et al., 2013). Ubiquitin are small heat shock proteins (see chapter 1.3.5) that link themselves to proteins that are to be degraded in the ubiquitin-proteasome pathway. Proteasomes are cellular organelles, whose main function is degrading proteins that are marked for destruction. Increased proteolysis occurs as a result of muscle regulations that lead to increased mRNA transcription of ubiquitin ligases such as atrogin-1/MAFbx and MuRF1, as well as raised levels of proteasomes (Sacheck et al., 2004; Sandri, 2008). This process is influenced by transcription factors known as Forkhead box O (FoxO). Four FoxO members are found in human skeletal muscle; FoxO1, FoxO3, FoxO4 and FoxO6, with the latter primarily found in the central nervous system (Sanchez, Candau, & Bernardi, 2014). FoxO1 and FoxO3 can inflate the transcription of ubiquitin ligases in the presence of factors known to induce atrophy (Lieber, 2010). On an opposite note, an increase in IGF-1/Akt signaling can translocate FoxO from the myonuclei to the cytoplasm (Sandri, 2008). Adenosine monophosphate-activated protein kinase (AMPK) activation is associated with increased nuclear translocation of FoxO1 and FoxO3, thus having an opposing effect to IGF-1/Akt (Sanchez et al., 2014). FoxO proteins are also involved in the autophagy-lysosomal pathway. Autophagy is a cellular

[12] C2C12: mammalian skeletal muscle models that can be used to study molecular processes involved in cell proliferation and differentiation (Yang & Goldspink, 2002).

housekeeping process involving lysosomes; cellular subunits that break down organelles, protein substrates and damaged cell material. FoxO3 controls the transcription of several autophagy-dependent genes, while the role of FoxO1 in autophagy remains enigmatic (Mizushima & Komatsu, 2011; Sanchez et al., 2014; Sandri, 2008). FoxO proteins are further implicated in regulating mitochondrial ubiquitin ligases, potentially affecting mitochondrial autophagy (mitophagy) (Sanchez et al., 2014; Schiaffino et al., 2013). Moreover, FoxO proteins can negatively regulate muscle regeneration by inhibiting satellite cell activation (Sanchez et al., 2014).

Myostatin, also known as GDF-8 (growth and differentiation factor 8), is produced by skeletal muscle and identified as a negative regulator of myogenic development and growth (reviewed in: Jespersen, Kjaer, & Schjerling, 2006). Myostatin can intercede post-natal hypertrophy by targeting satellite cell differentiation and proliferation through a process that results in a negative adjustment of myogenic transcription factors (MyoD, Myf-5, myogenin and Mrf4 proteins) (Matsakas & Diel, 2005; Walsh & Celeste, 2005; Zanou & Gailly, 2013). In addition to inhibiting satellite cell contribution to muscle growth, myostatin may also have direct effects on myotubes. Zimmers et al. (2002) observed muscle and fat wasting after injecting high levels of circulating myostatin into the thighs of mice, controlling for the potential effect of myostatin in inducing anorexia. Furthermore, Trendelenbrug et al. (2009) demonstrated that increased myostatin expression is accompanied by reduced diameter of *in vitro* human skeletal muscle myotubes. The authors further hypothesize that instead of activating catabolic pathways, myostatin may play a role in inhibiting processes that promote protein synthesis. However, the consequence of myostatin expression in *in vitro* may differ from what happens in living organisms since hormonal and growth factors are difficult to replicate in cell cultures.

2.2.4 Skeletal muscle, immune cells and inflammatory agents

Skeletal muscle can produce and secrete various cytokines and proteins, and is identified as an endocrine organ (Pedersen, 2011). Walsh et al (2011) imply that exercise can promote long-term anti-inflammatory effects. The effects are probably partly due to a training-induced reduction in visceral fat. In addition, each bout of exercise can induce a cytokine response that promotes an auto-inflammatory environment. Based on studies evaluating the effect of endurance training on inflammatory agents, the benefits of exercise on auto-inflammatory response are well established (Walsh et al., 2011). A systematic review aimed to explore the

potential effectiveness of resistance training on altering the serum concentration of certain cytokines. The meta-analysis supported resistance-training interventions in increasing adiponectin and decreasing leptin (see footnote 4 and 5) and serum CRP levels. Moderate to high levels of training duration, frequencies and intensities were necessary to provoke the changes in cytokine levels. Regarding TNF, there was a lack of significant changes following interventions with resistance training, possibly related to small sample sizes and low statistical power in the included studies (de Salles et al., 2010).

Circulating and local cytokine levels may fluctuate in response to internal and external stress factors. Examples of internal stress factors are hypoxia, mechanical stress, thermal stress, osmotic stress and oxidative stress as well as energy imbalance. External stress signals can indicate systemic stress and induce cellular responses (Welc & Clanton, 2013).

Increased expression of TNF and other pro-inflammatory cytokines can cause insulin resistance and curtail the IGF-1/PI-3K/Akt hypertrophic pathway. Additionally, they may also play a role in activating the NF-κβ-pathway, a process implicated in increasing proteolysis (Peterson & Guttridge, 2008; Sandri, 2008; Zanou & Gailly, 2013). NF-κβ transcription factors are usually kept in a dormant state by binding to an inhibitory protein called Iκβ. Pro-inflammatory cytokines can trigger Iκβ, leading to nuclear translocation of NF-κβ. Activation of NF-κβ in turn induces gene transcription of proteins and enzymes involved in inflammatory processes, creating a positive feedback loop (Barnes & Karin, 1997).

Inflammatory processes in skeletal muscle can rattle muscle homeostasis, although it is also recognized as a benign process in accelerating muscle repair and regeneration following injury or altered use. Generation of pro-inflammatory cytokines in inflamed muscle tissue leads to invasion of inflammatory cells such as neutrophils and macrophages. Neutrophils are white blood cells with a phagocytic function in clearing up damaged muscle fibers. However, neutrophil activation can release free radicals that can cause secondary harm to muscle tissue (Tidball, 2005). Succeeding the intrusion of neutrophils, macrophages are suggested to play a role in absorbing cellular debris. They can be divided into several subtypes that present at different times, suggesting that macrophages may have additional functions. For instance, macrophages are dense in pro-inflammatory cytokines, and macrophagal release of these cytokines may attenuate muscle regeneration. On the other hand, macrophages are also

implicated in helping satellite cells avoid apoptosis, thus possibly promoting muscle repair (Smith, Kruger, Smith, & Myburgh, 2008).

2.2.5 Regulators of muscle fiber function

Seeking to maintain normal cell function, muscle fibers can express heat-shock proteins (HSP) in response to elevated temperatures or other forms of physiological stress. HSP are also known as molecular chaperones and their expression is tissue-specific, with muscle fibers primarily displaying ATP-independent small HSPs as well as ATP-dependent HSP60, HSP70 and HSP90[13]. In addition to protecting the cell by preventing protein misfolding and aggregation, HSPs are involved in cell signaling by acting as molecular chaperones in transporting enzymes and proteins to organelles (Z. Li & Srivastava, 2004; Liu & Steinacker, 2001; Schlesinger, 1990). Ubiquitin is a small HSP expressed in muscle cells and is further commented on in chapter 2.2.3. Cellular stress can prompt translocation of a small HSP with a molecular weight of 27 kDA from the cytoplasm to the nucleus. The prime function of HSP27 is to protect muscle cells against oxidative stress and prevent apoptosis (Dubinska-Magiera et al., 2014). Located in the mitochondria, HSP60 take part in the transport and assembly of mitochondrial protein that are encoded by nuclear DNA (Liu & Steinacker, 2001). Cellular volume of HSP60 is proposed to be comparative to mitochondrial content, with a concomitant increase in citrate synthase[14] and HSP60 observed in rats after bouts of endurance exercise (Mattson, Ross, Kilgore, & Musch, 2000). In response to cellular stress, levels of the HSP70 family are inflated. Two forms of HSP70 are glucose-regulated (GRP75 and GRP78). GRP75 act in transporting and folding proteins in the mitochondria (Liu & Steinacker, 2001), while GRP78 is expressed in the endoplasmatic reticulum and involved in protein folding (Z. Li & Srivastava, 2004). HSC70 and HSP72 represent two other members of the HSP70 family. HSC70 are present in the cytoplasm in non-stressed conditions and act in maintaining intracellular homeostasis (Bozaykut, Ozer, & Karademir, 2014). However, a decrease in HSC70 was observed in the *m. soleus* during non-weight bearing in rats, implicating a possible role of HSC70 in regulating the rate of protein synthesis (Ku, Yang, Menon, & Thomason, 1995). Cytoplasmic synthesis of HSP72 is highly induced by heat. Besides aiding in transport of proteins to cellular compartments, HSP72 can prevent protein aggregation and promote refolding of partially folded proteins (Bozaykut et al., 2014). HSP90 constitutes another group of HSPs that are involved in stabilizing hormone receptors by binding to

[13] Classification of HSP is based on molecular mass in kilodalton (kDa)
[14] Citrate synthase is an enzyme that is often used as a marker of undamaged mitochondria

unoccupied receptors and keeping them in a quiescent state. HSP90 are involved in cell cycle regulation by retaining proteins in a folded form (Bozaykut et al., 2014; Liu & Steinacker, 2001; Sreedhar, Kalmar, Csermely, & Shen, 2004).

In addition to various physiological stress, physical exercise also has the potential of stimulating level of HSPs in skeletal muscle. Furthermore, pro-inflammatory cytokines may influence the expression of HSPs , possibly increasing susceptibility to apoptosis (Liu & Steinacker, 2001). Schett et al. (2003) observed a temporal decrease of HSP 70 synthesis in cell cultures treated with TNF. As discussed by the authors, a transient down-regulation of synthesis may curb the anti-apoptotic effect of HSP70. Increased levels of anti-HSP60 antibodies are observed in SpA, although this elevation may primarily reflect an activation of the general immune response (Hjelholt et al., 2013). A dated review upholds that although antibodies against HSP have been observed in different inflammatory, rheumatic diseases, levels of anti-HSP antibodies do not differ greatly from healthy subjects and the role of anti-HSP antibodies as a central autoimmune disease pathogen is unlikely (Tishler & Shoenfeld, 1996).

Metabolic processes produce small atoms or molecules called reactive oxygen species (ROS). Perturbations in cell redox state can lead to an increased production of ROS, potentially causing oxidative damage to muscle fibers. Superoxide and nitric oxide represent the prime ROS produced in cells. Superoxide is a mild oxidative, but can be catalyzed to form other biologically toxic ROS. Nitric oxide interacts with superoxide to produce an oxidizing agent named peroxynitrite. Superoxide dismutase (SOD) is one of three major antioxidant enzymes in cells, and protects the cell from the pro-inflammatory effects of superoxide by converting it to hydrogen peroxide and oxygen. Glutathione peroxidase (GPX) or catalase (CAT), two other antioxidant enzymes, then remove this (Afonso, Champy, Mitrovic, Collin, & Lomri, 2007). The amount of antioxidant enzymes differ between fiber types, with the highest relative amount in type 1 fibers. Endurance training can increase the cellular level of SOD and GPX, while the effect of exercise on CAT is uncertain (reviewed in: Powers et al., 2011). In contrast, pro-inflammatory cytokines associated with various joint diseases are proposed to repress antioxidant enzymes, resulting in an increase in ROS (Afonso et al., 2007). A 20-year old study observed elevated levels of serum nitrate, a marker of nitric oxide production, in patients with active SpA (Stichtenoth, Wollenhaupt, Andersone, Zeidler, & Frolich, 1995). Notably, the patient population included only one patient with AS, with the remaining

possibly affected more by peripheral joint inflammation than axial inflammation. Contradictory results are reported in a study where no difference in levels of nitric oxide or SOD was observed between untreated AS patients with active or non-active disease compared to age- and sex-matched controls. However, the latter study noted significantly higher levels of CAT as well as malondialdehyde, a marker of oxidative stress, in patients with active disease compared to controls. These findings may indicate that oxidative stress is increased in AS patients with active disease (Ozgocmen et al., 2004).

2.2.6 Possible effects of pharmaceuticals on body composition and muscle tissue

Pharmaceuticals have potential side effects, and the following passage will discuss how some of the disease-modifying medication commonly used by SpA patients may have an effect on muscle tissue or body composition.

As previously mentioned, use of NSAIDs are advocated as the basic medication for treatment of SpA. Long-term use of NSAIDs is associated with an increased risk of gastrointestinal and cardiovascular side effects (Braun et al., 2011). NSAIDs block cyclooxygenase (COX), and the various COX-inhibiting drugs are subgrouped based on their specificity to the main COX isoforms COX-1 and COX-2. Transcript of COX-1 increase following exercise, but is also bountiful at the constitutive level. Intramuscular level of COX-2 is low at rest, but increased expression is seen in response to stimuli such as injury or exercise. Common drugs such as ibuprofen and acetaminophen suppress both COX-1 and COX-2 and are considered to be non-selective COX-inhibitors (Trappe & Liu, 2013). COX is an enzyme that synthesizes prostaglandins; hormone-like mediators that stimulate protein metabolism (Alaranta, Alaranta, & Helenius, 2008). Indeed, the results of a double-blind placebo-controlled study indicate that consumption of non-specific COX-inhibitors at a maximal over-the-counter daily is associated with attenuated protein fractional synthesis rate following a bout of eccentric strength exercise (Trappe et al., 2002). The study did not measure the long-term effect of drug use on muscle metabolism, but hypothesize that regular use of these pharmaceuticals may inhibit muscle hypertrophy. Contrary to this, a double-blind randomized controlled trial involving 12 weeks of strength training in OA patients, observed no difference in muscle mass (CSA) between patients on NSAIDs (ibuprofen) vs placebo drugs (Petersen et al., 2011). Furthermore, enhanced muscle volume and strength has been observed in a group of older adults consuming acetaminophen or ibuprofen in combination with 12 weeks of strength

training (Trappe et al., 2011). The researchers propose that chronic use of COX-inhibiting drugs can lead to adaptations that advocate skeletal muscle hypertrophy in older individuals. Nonetheless, both OA patients and the elderly participants may have trained harder due to the pain-relieving effect of NSAIDs, thereby potentially influencing study results. Ingestion of NSAIDs is further suggested to have a deleterious effect on satellite cell activation by suppressing growth factor signaling (Mackey, 2013). Paulsen et al. (2010) examined the influence of a COX-2 inhibitor (celecoxib) on recovery and regeneration following eccentric exercise and observed no group difference in the number of satellite cells. Contradictory outcomes are reported in the previously mentioned study on OA patients, where the number of satellite cells increased in the placebo group, but not in the patients ingesting a non-specific COX-inhibitor (ibuprofen) (Petersen et al., 2011). These results coincide with an observed blunting effect of NSAIDs (non-specific COX-inhibitor; indomethacin) on satellite cell response in male endurance athletes following a single bout of 36 km running (Mackey et al., 2007). As concluded in a review article (Schoenfeld, 2012), there is a lack of compelling evidence showing that occasional use of NSAIDs has detrimental effects on muscle growth. However, the effect of long-time use is more elusive, particularly in regards to the possible effect on satellite cell activity. Mackey (2013) and Schoenfeld (2012) recommend a need for future research to elucidate the discrepant results as well as investigate the possible effects of age and training status on differential response to NSAIDs.

Pharmaceutics that function antagonistically to TNF, a crucial cytokine in rheumatic disease, are a rather novel therapeutic option in SpA and there are few studies investigating the effect of these medicines on muscle tissue. A 1-year prospective study suggests an association between anti-TNF treatment and a small, but significant gain in body weight and lean mass without shifts in fat mass (Briot, Garnero, Le, Dougados, & Roux, 2005). The authors propose that the observed changes relate to a 15% transient increase in serum IGF-1. Results of this study should however be interpreted with caution due to the small study population and lack of control group. Additionally, TNF blockers may ease common SpA symptoms such as pain, stiffness and fatigue (Machado et al., 2013), enabling the patients to be more physically active. The same research group examined changes in body mass (BM) and body composition in a larger group of SpA patients receiving anti-TNF-therapy in a 2-year prospective study. Interestingly, they observed a significant gain in BM after year 1 and 2, due primarily to an increase in FM as well as a small, but significant increase in LBM (Briot, Gossec, Kolta, Dougados, & Roux, 2008). Furthermore, a subsequential protocol to a subsample of the SpA

cohort from Briot et al., 2008 used new DXA software enabling separation of abdominal fat into visceral and subcutaneous adipose tissue. They observed significant gain in both visceral and subcutaneous FM, further questioning the relationship between these changes and risk of CVD (Hmamouchi et al., 2014). Diet and level of physical activity were not assessed in the aforementioned studies and are possible confounders to alterations in body composition. Thus, it is hard to explain if the changes in body composition are due to specific effects of anti-TNF medication or an effect on general well-being, physical activity and diet. However, the results reported in Hmamouchi et al. (2014) concur with the observed shifts in FM in a smaller 2-year prospective study, where no parallel change was detected in self-reported diet or exercise habits (Toussirot et al., 2014). On an opposite note, studies assessing the effect of 12 (Metsios et al., 2007) and 24 (Marcora, Chester, Mittal, Lemmey, & Maddison, 2006) weeks of anti-TNF medication in RA patients observed no significant changes in body composition. Collectively, the effect of TNF-blockers on body composition is conflicting and specific effects on muscle tissue appear uncertain.

Table 2. Studies evaluating effect of anti-TNF therapy on muscle tissue/body composition. Values are mean (SD) unless otherwise noted.

Author (year)	***Aim of study***	***n (age)***	***Measured variables***	***Results***	***Conclusion***	***Comment***
Briot et al. (2005)	Evaluate change in body weight and BC in SpA patients receiving anti TNF therapy over 1 year	19 SpA patients (range: 21-71)	Demographic data, VAS pain, BASDAI, BASFI, ESR, CRP, BC and BMD by DXA at baseline, 6 months and 1 year. Bone remodeling including IGF-1	At 6 months: BM: + 2.6 (3.7) %, p= 0.0012, LBM: + 2.1 (4.5) %, p= 0.03. At 1 year: BM: + 3.4 (4.69 %, p= 0.001, LBM: + 3.2 (4.2) %, p= 0.003. At 3 months: Increase in IGF-1: +15 (40) %, p= 0.04	Suggest changes in BC are related to anti-TNF therapy	Twelve patients previously treated with corticosteroids, three currently. No control group. No assessment of diet or PAL
Briot et al. (2008)	Evaluate change in body weight and BC in patients receiving anti TNF therapy (etanercept or infliximab) over 2 years	106 SpA/AS/ PsA patients (38±11)	Demographic data, VAS pain, BASDAI, BASFI, ESR, CRP, BC and BMD by DXA at baseline and once a year	At 1 year: BM: +3.4 (5.9) %, p < 0.001, FM: 12.1 (22.4) %, p< 0.001, LBM: 1.9 (5.2) %, p < 0.001. At 2 years: BM: +3.5 (7.1) %, p < 0.001, FM: 14.5 (26.8) %, p< 0.001, LBM: 2.0 (5.6) %, p < 0.001. Change between year 1 and 2 non-sign.	Increase in FM – recommend assessment of serum lipids in future studies Weight gain can be explained by specific effects of anti-TNF therapy and/or generic effects of inflammation control by anti-TNF	Standardized procedures. Possible confounder: increased PAL due to effect of medication on pain/stiffness. 33.9% with previous intake of steroids, 1% with current intake. 37.7% had no change in BM No specific analysis of fat distribution No control group (difficult to find)

Hmamao-uchi et al. (2014)	Evaluate changes in VAT and SAT visceral in patients with anti-TNF therapy. 2-year prospective study.	85 (39.3±11.4)- ancillary protocol to Briot et al. 2008	Baseline, 6, 12 and 24 months: waistline circumference, BM, BMI, VAT + SAT with DXA	VAT: at 6 months 13.2(20.5)%, $p <$ 0.0001, at 1 year 22.2 (28.2)%, $p <$ 0.0001, at 2 years 32.4 (36.6)%, $p <$ 0.0001; SAT: at 6 months 8.7(20.4)%, $p <$ 0.0001, 1 year 17.9 (29.4)%,, $p <$ 0.0001, at 2 years 24.2 (38.3)%, $p <$ 0.0001.	SpA patients initiating anti-TNF-therapy leads to significant increase in VAT and SAT	Effect of anti-TNF treatment can increase well-being → increased appetite. Ancillary protocol to published results – authors may have precipitated results? No assessment of diet or PAL
Marcora et al. (2006)	RCT: Evaluate effect of etanercept (TNF-inhibitor) on BC in patients with early RA. Randomized to 24 weeks of etanercept or methotrexate	26 (54±11 and 50±15)	Baseline, 12, 24 weeks: DXA, measures of physical function, DAS28, CRP, ESR, serum IGF-1, IGF-2, IGF-binding protein 3	Transient increase of IGF-1 at week 12, $p< 0.01$ No significant change in BC. Secondary analysis 6 months follow-up of patients who gained >3% BM: patients with etanercept gained more LBM (44% vs 14%), $p= 0.04$	Primary analysis shows no significant effect of TNF-inhibitor on BC	No assessment of PAL or diet
Metsios et al. (2007)	Evaluate effect of anti-TNF therapy on BC, PAL and protein intake	20 RA patients (61.1± 6.8) and 12 healthy controls matched for age, sex, BMI	Baseline, 2 and 12 weeks: Indirect calorimetry, BIA, IPAQ, DAS28, ESR, CRP, serum TNF	No significant change in LBM or FM.	TNF-blockers lead to improved disease activity and physical function + increased protein intake and PAL	BIA has lower validity than DXA
Toussirot et al. (2014)	Evaluate long-term consequence of TNF inhibitors on BC + short-and long-term effects of drugs on adipokine production (associated with anti-inflammatory effects) Single-center 2 year prospective study	12 SpA patients (40.7±4.6) 8 RA patients (60.5±3.4)	Baseline, 1,3,6,12,18 and 24 months: Demographic data, DAS28, HAQ, BASDAI, BASFI, ESR, CRP, venous blood samples (adipokines, ghrelin and insulin). DXA at baseline, 6, 12, 24 months	AS: gain total fat mass ($p= 0.02$), tendency for change in BM ($p= 0.07$). RA: significant changes for BMI ($p= 0.05$). AS + RA: Resistin levels decreased (-22.4%, $p= 0.01$)	TNF antagonists induce changes in fat mass; increased android fat – questions the impact of anti-TNF medication on cardiovascular risk	Total-body composition scan. Long duration, repeated measurements Small study sample Possible confounder: other medication (allowed to take corticosteroids, DMARDs, NSAIDs) Lack of control group

AS: Ankylosing Spondylitis**. BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index. **BASFI**: Bath Ankylosing Spondylitis Functional Index **BC**: Body Composition **BIA:** Bioelectrical Impedance Analysis. **BMD**: Bone Mineral Density. **BM**: Body Mass. **BMI:** Body Mass Index. **CRP:** C-reactive protein **DAS28**: Disease Activity Score in 28 joints**. DXA**: Dual energy X-ray absorptiometry **ESR**: Erythrocyte Sedimentation Rate. **FM:** Fat Mass. **HAQ**: Health Assessment Questionnaire. **IPAQ:** International Physical Activity Questionnaire. **LBM:** Lean Mass. **PAL**: Physical Activity Level. **PsA**: Psoriasis Arthritis. **RA**: Rheumatoid Arthritis. **SAT:** Subcutaneous adipose tissue. **SpA**: Spondyloarthritis. **TNF**: Tumor Necrosis Factor. **VAS**: Visual Analog Scale. **VAT:** Visceral adipose tissue.

Use of oral glucocorticoids, for example Prednisone, was defined as an exclusion criterion in our study. Glucocorticoids stimulate proteolysis and hinder protein synthesis, with a net catabolic effect that can lead to muscle atrophy (Mitch & Goldberg, 1996; Pereira & Freire de, 2011). Muscles with a predominance of fast fibers are more vulnerable to glucocorticoid-induced atrophy, while slow-twitch fibers are less susceptible (reviewed in: Schakman, Kalista, Barbe, Loumaye, & Thissen, 2013). There has been some uncertainty regarding the mechanisms governing glucocorticoid influence on muscle mass. A randomized, cross-over trial observed higher fasting glucose, amino acids, glucagon and insulin following short-term use of Prednisone vs. placebo. The authors suggest that the results implicate a blunting effect of glucocorticoids on the anabolic response to insulin (Short, Bigelow, & Nair, 2009). Occasionally used, medical treatment by use of systemic corticosteroids for SpA is not supported by evidence (Braun et al., 2011).

2.2.7 Mm. Quadriceps femoris

Encompassing *m. vastus medalis, m. vastus lateralis, m. vastus intermedius* and *m. rectus femoris, mm. quadriceps femoris* (QF) consists of rather short muscle fibers with high pennation[15] angles. Due to a large physiological CSA, QF is well suited in generating large forces (Lieber, 2010). Samples from the *mm. vasti* at the distal thigh of Caucasian cadavers indicate a considerable between-subject variability regarding vasti CSA, as well as an observation that each element of the vasti contributes to about one third of total vastus CSA. Moreover, the study investigators found a fused muscle mass in the distal part of QF in 30% of the cadavers, indicating that biopsies taken from *m. vastus lateralis* are susceptible to being interspersed with samples from *m. vastus intermedius* (Willan, Ransome, & Mahon, 2002).

QF, and more specifically *m. vastus lateralis,* is frequently used in research work as the preferred biopsy site in the lower extremities. Muscle biopsies play an important role in evaluating disease that may affect muscle tissue, and can be performed by open or needle technique (Mikell, Chan, Stein, Tanji, & Winfree, 2013). *M. vastus lateralis* is recognized as safe since main nerves and blood vessels are far away from the location of the biopsy, the site is tolerated well by study participants and there are limited cosmetic issues (Meola, Bugiardini, & Cardani, 2012; Mikell et al., 2013).

[15] Pennation angle: muscle fiber angle relative to the force-generating axis (Lieber, 2010)

Containing both slow- and fast-twitch fibers, *m. vastus lateralis* is a mixed striated muscle with a pooled estimated (mean±SD) 3.630±114 μm^2 fiber CSA and 50.3±1.9% type 1 fiber distribution in healthy individuals over 40 years old (Gouzi et al., 2013). For younger male individuals (21.5±2.4 years), the muscle fiber type distribution is reported to hierarchically descend from 2A>1>2X and CSA approximates to 4844±1286, 6174±1587 and 5160±1324 μm^2 for type 1, 2A and 2X respectively (Staron et al., 2000). In concordance with Simoneau & Bouchard (1989), the aforementioned studies report substantial interindividual variability in fiber type composition and CSA. Regarding myogenic precursor cells, analysis of 3,507 muscle fibers sampled from *m. vastus lateralis* in five healthy volunteers found no significant difference between the satellite cell population associated with type 1 fibers (0.067±0.01) and that observed in type 2 fibers (0.063±0.01) (Kadi, Charifi, & Henriksson, 2006).

2.2.8 Assessment of skeletal muscle strength and endurance

Exercise and recreational activities commonly rely on function in the lower extremities. Assessment of function in the knee extensors is common in studies on performance athletes, in pathological conditions, as well as in studies evaluating the effect of exercise interventions (McMaster, Gill, Cronin, & McGuigan, 2014; Park & Hopkins, 2013). Maximum strength is the maximum amount of force an individual can produce against an external load at a given time and can be evaluated trough different types of contraction (McMaster et al., 2014). A strong correlation between isometric and dynamic strength when tested with similar movements is reported in both athletes and recreationally trained men (McGuigan, Newton, Winchester, & Nelson, 2010; McGuigan & Winchester, 2008). Isometric testing is less available than 1 RM testing as it requires a force transducer and strain gauge, but is less vulnerable to confounding due to no change in joint angle and has been deemed highly reliable (McGuigan et al., 2010; McMaster et al., 2014). Estimating muscle strength by maximal voluntary contraction (MVC) relies on the test subject's ability to activate motor units. Evidence suggests that maximal voluntary activation is just slightly inferior to the true maximum evoked by supramaximal artificial stimulation of the nerve trunk or intramuscular nerve (Shield & Zhou, 2004). When measuring muscle strength by volition, familiarization of test subjects is important in order to eliminate false low values. Valid recordings of isometric MVCs should display a force plateau along with repeated attempts of low variability. Furthermore, standardized verbal cheering is advocated and test subjects should be given the opportunity to reject MVCs they do not consider as maximal attempts (Gandevia, 2001; Shield & Zhou, 2004; Wilson & Murphy, 1996).

Measures of maximum isometric strength allow us to explore peak force, mean force and explosive force production. Rate of force development (RFD) quantifies the "slope of the force time curve" (Wilson & Murphy, 1996 p. 20), and is a common measure of explosive strength. The RFD parameter may have an impact on function in activities requiring fast and forceful contractions, and an increase in RFD in *m. quadriceps femoris* has been observed after a period of progressive, heavy resistance training (Aagaard, Simonsen, Andersen, Magnusson, & Dyhre-Poulsen, 2002) and fast-velocity concentric strength exercise (de Oliveira, Rizatto, & Denadai, 2013). Contradictory results are reported by Oliveira et al. (2013), who detected no change in early or late RFD following isometric strength training. Mirkov et al. (2004) observed good reliability in repeated tests of RFD of elbow flexors (ICC= 0.81) and elbow extensors (ICC=0.87). However, evaluation of reproducibility of lower limb RFD by coefficient of variation indicates that measures of RFD are prone to relatively high method errors. In order to attain valid RFDs, familiarization and repeated attempts are recommended (reviewed in: Wilson & Murphy, 1996).

Muscular endurance or fatigue has no universal definition, but may describe the ability of skeletal muscles to perform repeated contractions against a sub-maximal load (Gandevia, 2001). There is no standardized method of assessment although different protocols have been used to evaluate muscle endurance (De Ruiter, Mallee, Leloup, & De, 2014; Sahin, Ozcan, Baskent, Karan, & Kasikcioglu, 2011). Muscle fatigue is believed to originate from both central and peripheral factors, with a common understanding that mechanisms of fatigue are essentially related to processes at the peripheral level (Allen, Lamb, & Westerblad, 2008). Central fatigue pertains to a reduction in the supraspinal stimulation of motoneurons, and can be influenced by a subject's ability to cope with exhaustion. As muscle fatigue arises, muscle receptors are subjected to a change in intracellular milieu. This may induce a shift in afferent signaling and a consequential reduced central drive of motoneurons (Gandevia, 2001; Westerblad & Allen, 2002). Release of Ca^{2+} by the sarcoplasmatic reticulum (SR) is pivotal in generating muscle contractions, and a reduction in Ca^{2+} concentration is considered an essential cause of peripheral muscle fatigue. Repeated muscle contractions against a sub-maximal load causes a gradual shift from aerobic energy consumption to anaerobic energy consumption. The result is a reduced pH-level due to accumulation of lactic acid. Often perceived as a substantial contributor to muscle fatigue, acidosis has limited effect on muscle contractions and probably plays a role in muscle fatigue by triggering central factors. Anaerobic energy consumption also involves cleavage of creatine phosphate to creatine and

inorganic phosphate (P_i). The latter compound reduces the myofibrillar responsiveness to Ca^{2+} as well as SR-release of Ca^{2+}, thus having a direct effect on muscle fatigue at the tissue level (Allen et al., 2008; Westerblad & Allen, 2002). Muscle fatigue is also influenced by the accelerated production of ROS caused by muscle activity. ROS scavengers are reported to reduce the rate of muscle fatigue, while increased levels of ROS are believed to negatively affect SR release of Ca2+ and Ca2+ sensitivity (Allen et al., 2008).

In a clinical setting, muscle fatigue arises along with an excessive feeling of discomfort and/or an inability to continue with the task given. Tests of muscle endurance explore the interplay of the required force, the maximum strength of the muscle(s) involved as well as fiber type distribution and metabolic capacity of the muscle cells (Allen et al., 2008).

2.3 Summary

SpA designates a group of inflammatory, rheumatic diseases characterized by axial and peripheral arthritis. Extra-articular manifestations are common, and patients report considerable relief of pain and stiffness following PA. The effect of chronic, systemic inflammation on muscle tissue is largely unknown. Studies evaluating muscle strength and body composition in SpA patients present conflicting results and the few reports examining muscle morphology are dated. As outlined in chapter 1 and 3 and in the research article, we sought to assess body composition, muscle strength and cellular variables in muscle tissue in SpA patients. We used immunohistochemical (IHC) assays to examine muscle fiber type distribution and muscle fiber CSA as well as number of myonuclei, satellite cells and leukocytes. The existence and amounts of proteins that determine muscle fiber size (chapter 2.2.3) as well as regulators of muscle fiber function (chapter 2.2.5) have not been investigated in the present study. In an attempt to gain more thorough insight regarding muscle tissue in SpA, we plan to further explore the collected muscle biopsies by western blot (immunoblot), an analysis that uses antibodies to detect specific proteins (Paciello & Papparella, 2009).

3. Material and method

3.1 Study sample

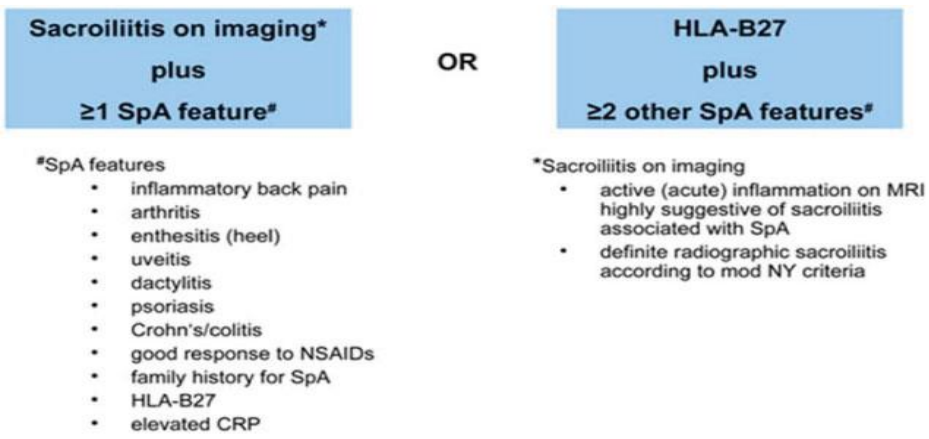
(See article for information on study inclusion and patient-control matching.)

Table 3. Inclusion and exclusion criteria for study participants with SpA

Inclusion criteria	Exclusion criteria
Age 30-45 years	Arthritis to the hip or knee joint or lower extremity injury within the last 12 months
Male gender	Myopathies
BMI 18.5-30	Cognitive impairment
SpA diagnosed by rheumatologist according to ASAS diagnostic criteria	Per-oral corticosteroid treatment
SpA symptoms ≥5 years	
Signed consent to participate	
Speaks Norwegian or English	

Recruited study participants had been diagnosed with SpA according to the ASAS classification criteria by a rheumatologist. Since there are no specific laboratory tests for SpA, the ASAS classification criteria can be used to classify SpA and are used for diagnostic purposes (Ehrenfeld, 2012; Rudwaleit et al., 2009).

Table 4. ASAS classification criteria (http://www.asas-group.org/education/ASAS-handbook.pdf)



Study participation was limited to the male gender. One reason is even though the prevalence gender difference is less than what was reported in earlier studies, the ratio still favors men (Lee et al., 2008). Several studies have shown less radiographic severity in female AS patients and a reported delay in diagnosis compared to male patients. It has also been reported that female AS patients have a higher prevalence of peripheral arthritis (Lee et al., 2008). If we had included female participants in this study, the additional age-range inclusion criteria would have left us addressing fertile women with SpA. The plausible use of oral contraceptives as well as physiological fluctuations in hormone levels due to menstrual cycles or pregnancy could pose as possible confounders to the dependent variables in this study (Oosthuyse & Bosch, 2010; Spangenburg, Geiger, Leinwand, & Lowe, 2012). Additionally, disease activity may change during pregnancy; from no change in symptoms to a marked improvement or a flare of disease activity (Lee et al., 2008), possibly accounting for some of the observed fluctuation in disease activity in female SpA patients of fertile age. By constricting our inclusion criteria to male patients with SpA, we hoped to reduce the influence of confounders and provide a more homogenous study sample. On the other hand, this weakens the external validity, as one cannot generalize results to apply for both genders based on studies where participation is limited to the male sex (Short, Yang, & Jenkins, 2013; Sørbye, 1996).

The desired age range of study participants was set to 30-45 years. In about 80% of the SpA patients the first symptoms present at an age younger than 30, and fewer than 5% of patients develop symptoms at older than 45 years (Braun & Sieper, 2007). Lower bound was set to 30 years in the hopes that this would increase the chance of including patients who have had SpA for some time. Adults are reported to lose only 5-10% of muscle mass up to 50 years of age, but show a marked decrease in muscle mass from age 50-80 (Hunter, McCarthy, & Bamman, 2004). The effect of age on skeletal muscle mass was explored in a study where MRI was employed to establish reference data for total and regional muscle mass in a large sample of men and women. Age was negatively correlated to muscle mass in the 45+ years age category, contrasting the non-relationship observed in the 18-44 years age category (Janssen et al., 2000). To reduce the chance of confounding results due to age-related changes like sarcopenia and loss of strength, the upper bound for age was set to 45 years in this study. Furthermore, since earlier recommendations on exercise in SpA focused on flexibility training (Dagfinrud et al., 2011), older SpA patients may have a history of less vigorous PA compared to healthy peers.

Control participants were recruited from hospital staff, friends or relatives of included patient participants as well as other acquaintances. Study inclusion and data collection was completed within the period *primo* September to *ultimo* November 2014.

3.2 Outcome measures

All participants completed questionnaires (att. 4 and 5) regarding age, level of education, occupational status and smoking behavior. In addition, habitual level of endurance- and strength exercise was self-assessed on a four-graded ordinal scale.

3.2.1 Disease-specific characteristics

All SpA participants completed the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) questionnaires (att. 4). BASDAI is an ASAS-endorsed, six-item, self-administered questionnaire. It is designed to measure patient-reported fatigue, back pain, peripheral joint pain, localized tenderness and morning stiffness on a scale ranging from 0 to 10. The sum of questions 1-4 is added to the average of questions 5 and 6. The total is then divided by 5 to give an average out of 10, with a BASDAI score of 4 or more often interpreted as active disease (Zochling, 2011). BASDAI is a convenient clinical tool with a mean time to complete of 67 sec and a test-retest reliability of r=0.93 (p<0.001) (Garrett et al., 1994). BASFI, a 10-item patient-generated index, was developed to monitor functional ability in AS patients. Eight questions concern self-assessed physical function, with the remaining two relating to the patient's capacity to cope with activities of daily life (Calin et al., 1994). BASFI has a low respondent burden taking less than three minutes to complete, and is recommended by ASAS to evaluate disease impact and for use in clinical trials (Zochling, 2011). Test-retest reliability within 24 hours is reported to r=0.89 (p<0.001) (Calin et al., 1994), although a low median score may suggest a floor effect (Ruof, Sangha, & Stucki, 1999).

Patient mobility was assessed by means of Bath Ankylosing Spondylitis Metrology Index (BASMI) (att. 6). This index was generated to provide clinicians with objective measures of primarily axial mobility in AS patients. Measures of cervical rotation, intermalleolar distance, tragus-to-wall distance, lumbar lateral flexion and lumbar flexion (modified Schobers) was graded on a 3-point scale from 0 to 2 in the first version of BASMI (Jenkinson et al., 1994). BASMI was later refined to a scale ranging from 0 to 10 (Jones et al., 1995), with the 11-point

version being more sensitive to change in disease activity (van der Heijde et al., 2012). Time to complete is estimated to 5 to 10 minutes, making it feasible in a clinical setting. It is also proposed by ASAS as the metrology index of choice in clinical trials. Interobserver reliability for the five metrology items is reported to range from r=0.94 (p<0.001) to r=0.99 (p<0.001) with similar high values for intrarater reliability (Zochling, 2011).

3.2.2 Muscle morphology

Muscle morphology was explored through muscle biopsy of the anterior thigh muscle. A competent researcher (professor Truls Raastad) with years of experience in biopsy sampling performed the biopsies.

Recurrent exercise induces progressive cellular remodeling in response to increased metabolic demands. In addition to physiological adaptation following repeated training, single bouts of exercise can lead to perturbations at the molecular level. For instance, muscle contractions can increase cellular levels of ROS, and resistance training is associated with alterations in cellular anabolic and catabolic pathways post-exercise (Egan & Zierath, 2013; Murton & Greenhaff, 2013). In order to eliminate potential acute effects of exercise on study variables, participants were asked to refrain from exercise for 48 hours in advance of the muscle biopsy.

Muscle tissue samples were obtained by use of the Bergström percutaneous needle technique (Dubowitz & Sewry, 2007; Mikell et al., 2013). The chosen site of biopsy was the midsection of *m. vastus lateralis*. With study participants in a supine position, the area around the biopsy site was draped and the skin and subcutaneous tissue was treated with local anesthesia (Xylocaine + adrenaline, 10 mg/ml +5 µg/ml; AstraZeneca, Södertälje, Sweden). A surgical blade was employed to make a 1-2 cm incision through the skin and muscle sheath. Antiseptic swabs were used to clean and apply pressure to the incision site until any bleeding stopped. A 6 mm Pelomi needle (Albertslund, Denmark) with an assembled sliding cannula and closed cutting window was then inserted 2-3 cm along the muscle belly. The cannula window was then opened and suction was applied, causing the muscle to bulge into the open cutting window. In concert with manual suction, muscle tissue was then obtained by twice closing the cutting window. The procedure entails a feeling of deep pressure within the muscle belly as well as a twitching sensation when the sample is cut (Dubowitz & Sewry, 2007; Meola et al., 2012). Upon completion of the biopsy, the skin edges were closed by three strips and dressed with an adhesive plaster. A compression bandage was applied to reduce the intramuscular

haematoma. Participants received information on wound care (att. 7), and a follow-up telephone call was made the next day to address any questions and potential complications.

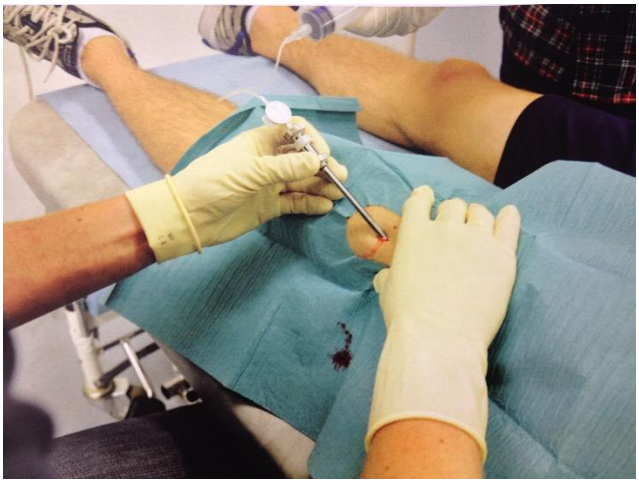


Figure 1. Muscle biopsy

Tissue sampling, immunohistochemical analysis and image analysis

(See article)

Microscope

A light source (EXFO, X1120PC-Q, Canada) connected to a light microscope (Olympus BX61, Tokyo, Japan) was used to quantify the stained biopsy sections. Pictures of marked dissections were taken by a digital camera (Olympus DP72, Tokyo, Japan) linked to the light microscope and analyzed by Cell-F software (Olympus, Tokyo Japan) for Windows XP (Microsoft, USA).

3.2.3 Muscle function

(See article for complementary information on testing procedure).

Muscle function of QF was evaluated as maximal strength by means of isometric knee extension. The maximal number of repetitions sustained with a submaximal load assessed muscle endurance capacity.

Prior to testing of maximal voluntary contraction (MVC), all participants performed five min of warm-up on a stationary bicycle at 100 watt and 60 rpm (Monark 839 Ergomedic, Vansbro, Sweden).

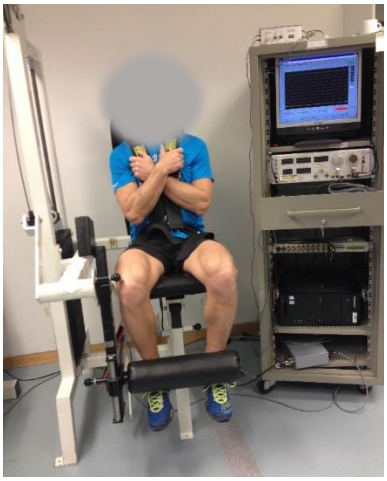


Figure 2. MVC test

Test conductor was aware of group membership of the subjects being tested. In an attempt to reduce possible bias, every study participant was vocally encouraged to exert maximal effort. Furthermore, a similar phrase was used for each attempt at MVC (e.g. *"1-2-3 – Give it your all! – hold – hold – hold – relax".*

Table 5. Examined variables of muscle function in mm. quadriceps femoris

Variables	Right leg	Left leg
Maximal isometric force (Nm)		
Rate of force development (RFD)		
Number of repetitions at 30% of MVC		
Total workload (number of repetitions x kg)		

3.2.4 Body composition and muscle mass

DXA

DXA (Lunar iDXA, GE Healthcare, Buckinghamshire, United Kingdom) was used to measure body composition. Entering the clinical scene about 30 years ago, the DXA was primarily designed to asses bone mineral density (BMD) in bone disease like osteoporosis. However, transmission of X-rays through the body at high and low energies allows the DXA to measure not only BMD, but also total body and regional distribution of LBM and FM (Andreoli et al., 2009). Modern DXA software allows for separate measures of FM into gynoid and android FM. A study evaluating the reliability of the Lunar iDXA observed a

coefficient of variation of less than 1% for all body composition measures except for android fat with a precision error of 2.32% (Hind, Oldroyd, & Truscott, 2011). Measurement errors may be due to technical errors in measurement or biological variation like hydration status. Exercise and intake of food and fluid can lead to small measurement changes for values of body composition (Nana, Slater, Hopkins, & Burke, 2012, 2013). Consequently, we advised the study participants to fast for a minimum of four hours and refrain from exercise for 48 hours leading up to the DXA scan.

Prior to the DXA scan, participants were asked to undress to their underwear and t-shirt, and height and weight was recorded on a stadiometer (Seca 217, Seca gmbh & co. kg., Hamburg, Germany). Next, study participants lay supine on the DXA scanning table with the ankles and knees held together by ankle- and knee support bands. Arms were held to the side with palms turned towards the hips and thumbs facing upward. Participants were asked to lay still for the approximately 10 minutes duration scan. We used the total body scan mode determined by the manufacturer and all scans were analyzed using enCORE Software, Version 14.10.022 (GE Healthcare, Buckinghamshire, United Kingdom). Two separate operators performed scans and analyses.

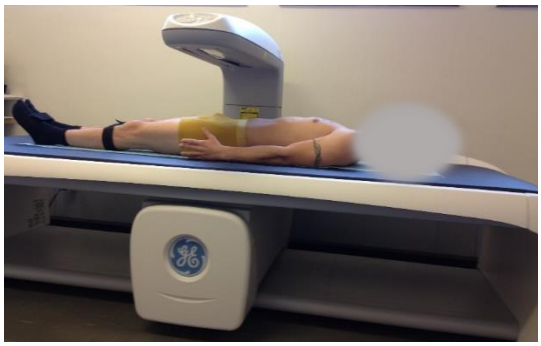


Figure 3. DXA scan

MRI

In addition to computed tomography (CT), the MRI is non-invasive and considered the gold standard in assessing regional body composition, with MRI having the advantage that it does not involve exposure to radiation (Andreoli et al., 2009; Tothill & Stewart, 2002). The MRI provides us with photographic slices of the region of interest that we can further analyze for CSA and volume of thigh muscles (see chapter 1.3.2) (Mijnarends et al., 2013; Tothill & Stewart, 2002).

All participants underwent magnetic resonance imaging (MRI) (Avanto TIM 76x18, Siemens, Erlangen, Germany) of the thigh at a private radiology center (Curato Røntgen, Oslo, Norway). Muscle CSA can vary throughout the muscle belly, and multiple measurements throughout the length of the muscle are advocated to achieve valid records of CSA (Raastad et al., 2010). The individual length of the femur bone was recorded as the mean of two attempts. This value was further applied to calculate the gap distance between the fifteen images obtained by a standardized MRI protocol (see article for scanning protocol).

Images were produced by Siemens software (WB19, Siemens, Erlangen, Germany) and analyzed using OsiriX imaging software (Pixmeo, Geneva, Switzerland). Image nr. 1 was excluded on all participants due to difficulty in identifying the various muscle bellies at the level of the lower pelvis. Image nr. 14 and 15 were also excluded from analyses as they were taken at the level of the upper epicondyles and tibiofemoral joint, and failed to depict QF tissue. The muscle bellies of vastus medialis, vastus intermedius, vastus lateralis and rectus femoris were outlined in the anterior compartment on the remaining 12 images, and used to estimate total volume of QF as well as maximum and mean CSA. M. sartorius was indistinguishable to the belly of QF on a proportion of the upper images. Consequently, we decided to include CSA of m. sartorius on image 2 and 3 for all participants. When in doubt, an anatomical atlas was consulted (Sobotta atlas of human anatomy, 2006). Regarding control participant nr. 5, image nr. 2 did not present measurable muscle tissue, and CSA for this image was extrapolated from image 3 using the mean image 2/image 3 ratio from the remaining study participants. As to control participant nr. 9, images were compressed around the mid-section of the femur and lacked images of muscle tissue surrounding the proximal and distal femur. To account for this shortfall, two separate images from the midportion of the femur were excluded from CSA analysis. Image nr. 2 and 13 were extrapolated from neighboring images using the mean ratio from the other study participants.

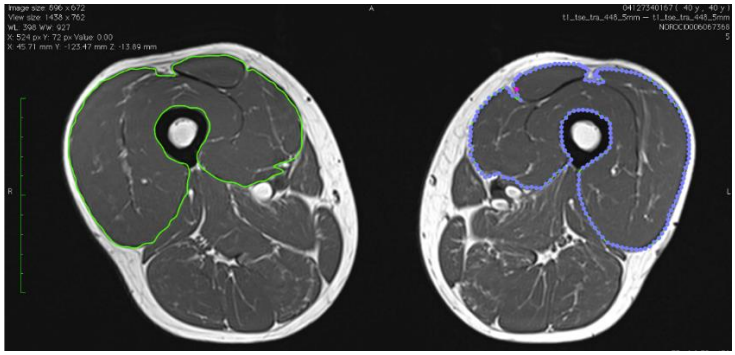


Figure 4. Magnetic resonance images of the right and left thigh with the muscle bellies of QF outlined. Muscle presents as dark tissue, adipose tissue is light.

3.3 Ethical considerations

Concealing private information in the data collected was attained by limiting data access to the master student and supervisors, and by storing the records in a secure database.

3.3.1 Potential risks and benefits for individual participants

Participants were provided with information of potential risks and discomfort prior to giving written consent (att. 2 and 3). We assessed the potential risks of participating in the study to be low and transient. Physical risks were minimized by carefully following measurement protocols and by assuring that individuals involved in research procedures were well trained. However, some study participants experienced tenderness during and after the muscle biopsy as well as concurrent or delayed muscle soreness associated with testing of muscle function. The DXA and MRI required that the participant lay still for 10-15 minutes and evoked discomfort in some of the SpA patients who often experience axial stiffness when immobile.

Participants did not receive monetary compensation, but were thoroughly informed of the results of their individual tests upon completion of the study.

3.4 Methodological considerations

Planning and completing a clinical study for the first time is a remarkably educational process. Certain methodological choices were made in advance of study outset based on presumptive obstacles. In retrospect, additional adjustments may have improved the quality of the study.

3.4.1 Research design

The study design is a small cross-sectional study. An observational research design allows us to observe patients from a usual clinical practice and possibly emphasize certain characteristics in those affected by disease (Grimes & Schulz, 2002c). If the results of this study favor the alternative hypothesis, we may infer a possible association between the presence of SpA and muscle morphology, muscle function or appendicular lean mass. However, cross-sectional studies examine outcome and exposure at the same time, rendering it incorrect to translate an observed temporal association into a causal relationship (Grimes & Schulz, 2002a).

The choice of study design allowed a sub-group of patients with SpA to be examined at one point in time in terms of muscle morphology, muscle function and muscle mass. Patients with an inflammatory, rheumatic disease often fluctuate in terms of disease activity and self-reported pain and stiffness. In this study, repeated tests of dependent variables would have enhanced the validity and reliability of the tests. Additionally, extending the time course of tests may have allowed for the inclusion of natural fluctuations, thus providing more precise estimates of the dependent variables (Laake, Olsen, & Benestad, 2008). Repeated tests would however require a higher degree of motivation and co-operation from study participants as well as increased time- and financial resources.

We did not define one main variable that we wished to explore and did not estimate the number of study participants by systematic sample size calculation. The aim of this study was to provide insight into a somewhat unexplored subject, and possibly observe tendencies that may further be tested with larger study samples or a different study design. Sample size was determined based on experience from other studies with similar outcome measures as well as assuring feasibility within the scope of a master thesis. Small studies are often deemed to lack statistical power (Whitley & Ball, 2002), and the modest number of participants in our study (n=20) may have inflated the risk of type 2 errors.

3.4.2 Bias and confounding

Those who opt to participate in clinical research have a tendency to be healthier than non-volunteers, thereby potentially reducing the external validity of the study (Grimes & Schulz, 2002b). Upon completing this study, we are left with the impression of higher levels of physical activity amongst the enrolled participants compared to the general population.

Additionally, the patients included had low to moderate disease activity as reported by BASDAI. Patients receiving anti-TNF medication had normal serological inflammatory markers, although they reported previous cycles of high disease activity. A clinical trial with an aim of observing potential differences in training response between SpA patients and controls could perhaps recruit a study sample that is more representative to the general SpA population.

In addition to recruiting patients and controls within the same age group, we made an effort to match pairwise by means of BMI and level of physical activity. BMI is a tool that is often used in epidemiological research to observe the association between adiposity and risk of disease (Flegal, Kit, Orpana, & Graubard, 2013). However, BMI cannot discriminate between LBM and FM. Metabolically healthy people with enhanced muscle mass can be misclassified as overweight when using BMI. In parallel, individuals with low LBM and an increased FM can have normal BMI (Oliveros, Somers, Sochor, Goel, & Lopez-Jimenez, 2014). Consequently, we aimed at matching patients and controls on self-reported level of physical activity. Subjective measures of physical activity can however be influenced by different interpretations and recall bias. They are not regarded as entirely valid when compared to objective measures such as the criterion method doubly-labeled water (Vanhees et al., 2005; Westerterp, 2009). Although level of physical activity and physical fitness are closely related, physiological adaptations to exercise can vary among individuals (Blair, Cheng, & Holder, 2001; Bouchard & Rankinen, 2001; Petrella et al., 2008). Thus, despite pairwise matching by self-reported amount of endurance- and resistance training, considerable differences between patients and controls in regards to physical fitness may have gone unspoken.

All patients were currently on various NSAIDs or TNF-blockers. As discussed in chapter 2.2.6, the effect of assorted medications commonly used in SpA on body composition and muscle tissue is unknown, and we cannot discard the possibility that pharmaceuticals may have influenced the outcome variables. We did not assess food intake among the study participants. Diets high in protein can have a positive effect on body mass and body composition (Westerterp-Plantenga, 2003) and we cannot dismiss a possible confounding effect of divergent food intake. Even though study participants were similar in regards to working full-time, we did not account for type of employment, nor for recreational activities spare endurance- and strength training. The amount of time spent on activities of daily living

at low and moderate intensities can affect total energy expenditure (Westerterp & Plasqui, 2004), and we cannot preclude the impact of work and lifestyle on body composition.

The laboratory technician who analyzed the biopsies and the operator who analyzed the DXA scans were aware of group membership, but not familiar with the disease in question. Accordingly, they were probably unsuspecting as to what tendencies to be alert to. Measures of muscle function and all statistical analyzes were performed by the master student who was aware of group membership and insightful regarding SpA disease. Although attempts were made to standardize all measurements, it is conceivable that knowledge of group membership may have influenced the outcome variables.

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Article

TITLE: *Reduced appendicular lean body mass, muscle strength and size of type 2 muscle fibers in spondyloarthritis vs. healthy controls: A cross-sectional study.*

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ABSTRACT

Objective: The effect of chronic, systemic inflammation on muscle tissue is largely unknown. The purpose of this study was to investigate body composition, muscle function and muscle morphology in patients with spondyloarthritis (SpA).

Methods: Ten male SpA patients (mean ±SD age 39 ±4.1 years) were compared with ten healthy controls matched for age, body mass index and self-reported level of exercise. Body composition was measured by dual energy X-ray absorptiometry. Quadriceps femoris (QF) strength was assessed by maximal isometric contractions prior to test of muscular endurance. Magnetic resonance imaging of QF was used to calculate specific muscle strength. Percutaneous needle biopsy samples were taken from *m. vastus lateralis.*

Results: SpA patients presented with significantly lower appendicular lean body mass (LBM) (p= 0.02), but there was no difference in bone mineral density, fat mass or total LBM. Absolute and specific strength of the left QF was significantly lower in SpA patients (p= 0.01 and 0.04) with a parallel trend observed for the right leg. Biopsy samples from the SpA patients revealed significantly smaller cross-sectional area (CSA) of type 2 muscle fibers (p= 0.04), but no difference in CSA type 1 fibers.

Conclusion: Results indicate that the presence of SpA disease is associated with reduced appendicular LBM, muscle strength and type 2 fiber CSA. Further research is needed to investigate whether catabolic pathways are up-regulated in SpA patients. Strength training may be an effective countermeasure against these negative effects on muscle indicated in SpA patients.

INTRODUCTION

The term spondyloarthritis (SpA) constitutes a group of related inflammatory, rheumatic diseases with Ankylosing Spondylitis (AS) often viewed as the most severe subtype. Hallmark clinical features are inflammatory back pain, peripheral arthritis and enthesopathy along with extra-articular manifestations such as uveitis, psoriasis and inflammatory bowel disease (1, 2), and an increased risk of cardiovascular disease (3, 4). Depending on the prime disease manifestations, patients are subgrouped into *axial* SpA for those presenting with a predominant involvement of the spine or sacroiliac joints or *peripheral* SpA (5, 6).

In addition to optimal pharmaceutical treatment, supervised and individually tailored exercise is advocated as the essential treatment for SpA (7). Furthermore, recent studies on SpA patients indicate that high-intensity endurance exercise can ameliorate traditional cardiovascular risk factors without causing a flare-up in disease activity (8, 9). For optimal health effects, a combination of both endurance and strength exercise is advocated for the general population (10). However, a systematic review on exercise interventions in SpA identified a lack of clinical trials with muscle strength training protocols that adhere to the American College of Sport Medicine recommendations (11).

Studies have demonstrated a possible negative effect of inflammatory processes on muscle tissue (12-14). SpA patients often describe beneficial effects of physical activity (PA) on pain and stiffness (15), indicating a possible direct involvement of muscle tissue in SpA (16). Lower muscle strength in SpA patients compared to healthy controls is reported (17-19), although normal level of muscle force is also described (20). Regarding body composition, reduced lean body mass (LBM) and/or shifts in fat mass (FM) are observed in SpA patients compared to controls in a few cross-sectional studies (19, 21, 22), but discordant results have also been published (23-26). At the level of local muscle tissue, dated studies observed mild to moderate histological abnormalities in AS patients (16, 27, 28). To our knowledge, there is a lack of novel studies examining muscle morphology in SpA. Likewise, there is a paucity of studies simultaneously addressing body composition, local muscle mass and muscle strength in this patient population. In addition to variables pertaining to body composition and muscle force, we aimed to utilize immunohistochemical analysis (29) to assess muscle fiber type distribution, myofiber size and myonucelar domain as well as number of satellite cells and leukocytes. Thus, the purpose of this exploratory cross-sectional study was to test the hypothesis that the presence of SpA disease may be associated with reduced LBM and/or muscle strength. We further hypothesized that muscle biopsies yielded from SpA patients

display manifestations of inflammatory disease and abnormal muscle morphology in comparison to healthy controls.

MATERIALS AND METHOD

Participants

A sample of 10 male patients with axial SpA according to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria (30) were recruited from the out-patient clinic from the Rheumatology unit at Diakonhjemmet hospital, Oslo and from patient organizations. Additional inclusion criteria were SpA symptom duration ≥5 years, age 30-45 years and body mass index (BMI) (kg/m^2) 18.5-30. Arthritis to the hip or knee joint or injury to the lower extremity in the past 12 months were considered exclusion criteria in addition to neuromuscular disease, cognitive impairment and a current or previous history of per-oral corticosteroid treatment. A convenient sample of 10 healthy controls fitting the same relevant inclusion criteria were enrolled in the study and pairwise matched to the patients by BMI and self-reported level of endurance-and strength training. The study was approved by the Regional Ethics Committee and all procedures were performed according to the Helsinki declaration (31). Participants were provided with oral and written information concerning the study and signed a written consent form before enrolling in the study.

Subject characteristics

All participants completed a questionnaire regarding age, level of education, occupational status and smoking behavior. In addition, habitual level of endurance- and strength exercise was self-assessed on a four-graded ordinal scale and preferred type of exercise was registered by verbal interview. Regarding SpA participants, Human Leukocyte Antigen (HLA) B27 phenotype, disease symptom duration and time of diagnosis was collected from the patients. Disease activity was evaluated by serum blood samples analyzed for C-reactive protein (CRP) and Eryhtrocyte sedimentation rate (ESR) (32). In addition, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a self-reported questionnaire, was used as a measure of subjective disease activity (33). Physical burden of disease was self-assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) (34). Axial mobility was recorded by an experienced physical therapist (KRN) using the 11-step Bath Ankylosing Spondylitis Metrology Index (BASMI) (35-37).

Measurements

Body composition

Measures of body height and weight were recorded on a stadiometer (seca 217, seca gmbh & co. kg., Hamburg, Germany) and used to calculate BMI. Dual energy X-ray absorptiometry (DXA) (Lunar iDXA, GE Healthcare, Buckinghamshire, United Kingdom) and enCORE Software (Version 14.10.022, GE Lunar) was used to estimate total and regional distribution of LBM and FM, including dispersion of android and gynoid fat. Appendicular skeletal muscle mass (RSMI) was predicted by the Baumgartner-equation (38): RSMI= (tissue mass arms) + (tissue mass legs)/ (height[m])^2. To reduce the possibility of measurement error due to biological variation in hydration status (39, 40), participants were asked to fast for a minimum of four hours and refrain from exercise for 48 hours leading up to the DXA-scan.

Quadriceps femoris (QF) volume and cross-sectional area (CSA)

All participants underwent magnetic resonance imaging (Avanto TIM 76x18, Siemens, Erlangen, Germany) of the thighs at a private radiology center (Curato Røntgen, Oslo, Norway). The scanning protocol consisted of three localizer scans for positioning, a T1-weighted turbo spin echo (TSE) sequence (15 slices of 5 mm thickness (1/15-15/15 of femur length), repetition time (TR) 432 ms, echo time (TE) 9,2 ms, field of view (FOV) 450 x 337,5 mm, voxel size 1x1x5 mm, TSE factor 5). Fifteen images were produced by Siemens software (WB19, Siemens, Erlangen, Germany) and analyzed by a viewing tool (OsiriX Imaging Software, Pixmeo, Geneva, Switzerland).

Image nr. 1 was excluded on all participants due to difficulty in identifying the various muscle bellies at the level of the lower pelvis. Image nr. 14 and 15 were also excluded from analyses as they were taken at the level of the femur epicondyles and tibiofemoral joint, and failed to depict QF tissue. The perimeter of the muscle bellies in the anterior compartment of the thigh was manually outlined as region of interest (ROI) on the remaining twelve images. Interpolation at intervals of 1:15 femur length distance was used to estimate total volume of QF. Mean QF CSA was computed by averaging the volume of all twelve ROIs and maximum QF CSA was determined by identifying the largest ROI captured.

Muscle function

Succeeding a five-minute warm-up protocol on a stationary bicycle (Monark 839 Ergomedic, Vansbro, Sweden), maximal voluntary contraction (MVC) of the knee extensors was measured at 90º knee angle using an isometric knee-extension device (GYM 2000 AS,

Vikersund, Norway). Participants were stabilized in the apparatus with straps secured over the hips and shoulders and settings adjusted to ensure a 90º angle at the hip and knee joints. The lever arm of the knee-extension device with an attached force transducer (HBM U2AC2, Darmstadt, Germany) was individually adjusted so that the contact point with the participant's calf was just proximal to the line of the medial malleolus. Participants began with three incremental bilateral isometric test contractions to familiarize with the testing procedure (41). Succeeding the warm-up protocol, the participants performed three unilateral maximal isometric contractions. Each contraction lasted for five sec, with 60 sec recovery time interspaced between each attempt. The right leg was tested first on all participants, followed by the left leg. Participants were instructed to attain maximal force as quickly as possible and MVC torque (Newton meter –Nm) and rate of force development (RFD) was recorded from the best trial. LabView software (National Instruments Corporation, Austin, TX, USA) was used for data acquisition and inspection of time-force curves. Specific muscle strength (maximal voluntary torque pr. unit muscle) was calculated as the MVC Nm/total QF volume ratio and MVC Nm/max QF CSA ratio.

Following the MVC tests, the participants completed a test of muscular endurance. They were asked to perform as many repetitions of knee extension as possible with a resistance of 30% of MVC. Each repetition was performed at the pace of a metronome (Korg metronome MA-30, China) with one second in the concentric phase and one second in the eccentric phase. Initiating the movement with 90 degrees of flexion in the knee, the knee was fully extended and then lowered back to the starting position. Fatigue was defined as the inability to fully extend the knee at the pace of the metronome for three consecutive repetitions. A hand tally counter (Clas Ohlson, Insjön, Sweden) registered the total number of repetitions. Total workload (number of repetitions x kg) was then recorded.

Muscle morphology

Biopsy handling

In an attempt to eliminate the acute effects of exercise on study variables (42, 43), participants were asked to abstain from exercise for 48 hours prior to muscle tissue sampling. With participants in a supine position, the muscle biopsy was obtained under local anesthesia (Xylocaine + adrenaline, 10 mg/ml + 5 µg/ml; AstraZeneca, Södertälje, Sweden). A percutaneous biopsy was taken from the midsection of *m. vastus lateralis* using a 6 mm Pelomi needle (Albertslund, Denmark) with manual suction and a double-chop method. The

same person completed all muscle biopsies, and attempts were made to collect the samples from the same tissue depth. A total of approximately 100-150 mg tissue was obtained and further divided into specific pieces for immunohistochemistry (finest bundles, 30-40 mg) and homogenization (1-2 x 50 mg). Following excision, tissue samples were rinsed prior to being frozen in isopentane on dry ice and stored at -80ºC until further analysis.

Immunohistochemical analysis:

Tissue samples were thawed to -20ºC and serial 8-µm thick sections were cut using a microtome (CM 1860 UV, Leica Microsystems; Nussloch, Tyskland), and mounted on microscopic slides (Superfrost Plus, Thermo Scientifi, MA, USA). Muscle sections double stained (see appendix) for SC71/Dystrophin were blocked for 45 min with 1% BSA (bovin serum albumin; Cat#37525, Thermo SCIENTIFIC, USA), and Pax7/Laminin for 10 min with a protein-blocker (Cat#X090930-2, Protein Block, Serum Free, Ready–To–Use, Denmark) before incubation with appropriate primary antibodies (see appendix) diluted in blocking solution either overnight at 4 °C (SC71/dystrophin, CD68/dystrophin, CD66b/dystrophin) or 60 min in room temperature (Pax7/Laminin). Monoclonal antibodies against Pax7 were used to visualize satellite cells, CD68 and CD66b to visualize leukocytes (macrophages and neutrophils respectively), SC71to visualize fiber type distribution (MHC II) and polyclonal antibodies against laminin and dystrophin to identify cellular position (Image 1 and 2).

Slides were thereafter washed 3 x 10 min in 0.05 PBS- t solution and incubated for 45 min with an appropriate secondary antibody (see appendix), washed again 3 x 10 min in 0,05 PBS-t solution, coated with a coverslip and glued with ProLong Antifade Reagent with DAPI (Cat#P36935, molecular probes, Life Technologies, USA) and left to dry overnight at room temperature. A high- resolution camera (DP72, Olympus Corp., Tokyo Japan) mounted on a microscope (BX61, Olympus Corp., Japan) with a fluorescent light source (X-cite 120PCQ; EXFO Photonic Solutions Inc., Mississauga, ON, Canada) was used to visualize and take pictures of the muscle sections.

Image analysis:

The number of fibers and positive cells were manually counted by marking each fiber and positive cells on a blueprint (Black-white photos taken with 4x magnification) with a pen while simultaneously pressing a turnstile (Laboratory Counter). Muscle fibers cut longitudinally, fibers with fractured membranes and fibers with unclear staining were

excluded from further analysis. The counted muscle fibers were used to determine the number of satellite cells, CD68 and CD66b positive cells per muscle fiber and per fiber phenotype.

The counting criterion for satellite cells was co-localization of Pax7 and DAPI staining within the laminin staining showed in image 1. Both intracellular and extracellular leukocytes (macrophages and neutrophils) were quantified by counting criterion of co-localization of DAPI staining and CD68 or CD66b, and whether the positive cells were located inside or outside dystrophin staining (Image 2A and B).

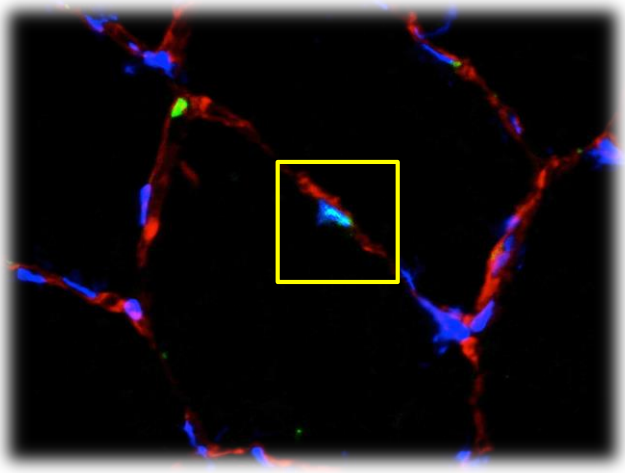

Image 1. Pax7 positive cell (satellite cell) inside the yellow square. Red stain = laminin, green stain = Pax7 = and blue stain = DAPI (nuclei)

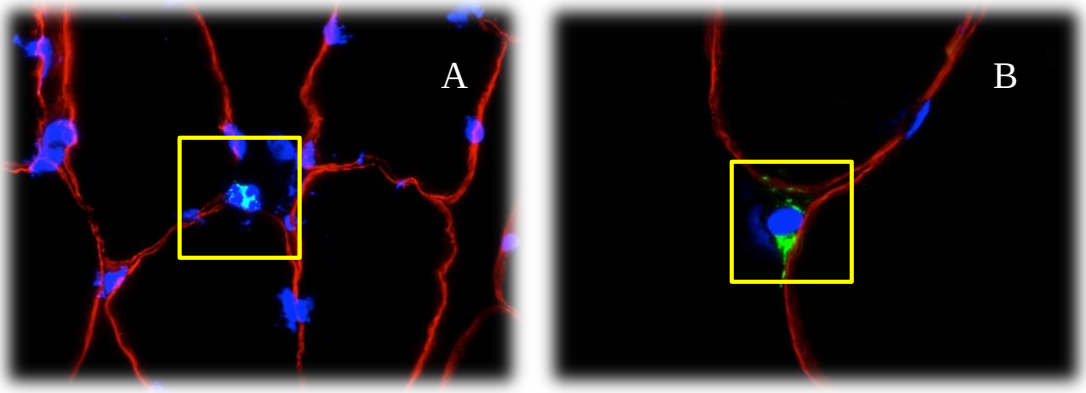

Image 2. A: CD66b positive cell (neutrophil granulocyte) inside the yellow square. Red stain = laminin, green stain = CD66b and blue stain = DAPI (nuclei). B: CD68 positive cell (macrophage) inside the yellow square. Red stain = laminin, green stain = CD68 and blue stain = DAPI (nuclei).

Myonuclei were analyzed with ImageJ using Fiji image and Cell counter processing package (http://fiji.sc/Cell_Counter) (Image 3A). To achieve satisfactory statistical power, 50 muscle fibers of each fiber type were included in the analysis (44). DAPI staining with the geometric

center within the dystrophin stain was defined as myonuclei (Image 3B) (45). Myonuclei are presented as number per muscle fiber and myonuclear domain was calculated by dividing the number of myonuclei by muscle fiber CSA.

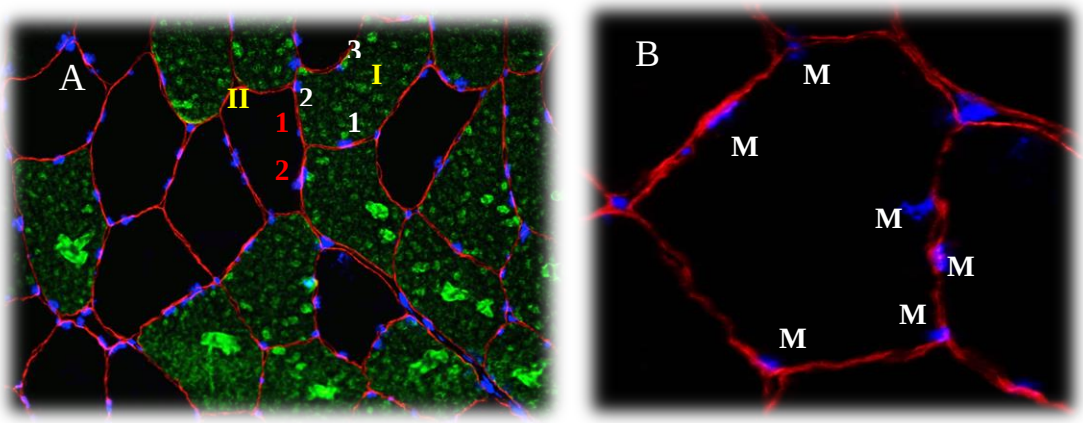

Image 3. A: Counting myonuclei. Biopsy marked with dystrophin (red stain), MHC II (green stain) and DAPI (blue stain). Roman numerals indicate fiber type I and II. White numbers mark myonuclei in type I fibers and red numbers for type II fibers. B: Blue Stain = DAPI (myonuclei) and red markings = dystrophin. Myonuclei branded with M were determined to have its geometric center (nucleus center) inside the dystrophin labeling.

TEMA (ChekVision, Hadsund, Danmak) was used to analyze the intensity of SC-71 staining for fiber type determination, and fiber CSA was analyzed by calculating the area within the dystrophin staining (Image 3).

Statistical analyses

Statistical analysis and tests were carried out using SPSS (version 21, IBM, Armonk NY, USA) and GraphPad Prism (version 6, GraphPad Software, La Jolla CA, USA). Descriptive statistics were calculated for each outcome variable and presented as mean with standard deviation and minimum and maximum values. Preliminary analysis checked for normality of all variables by visual inspection of histograms and the Shapiro-Wilk test. To analyze patient-control differences, normally distributed variables were compared using paired samples t-test. Skewed variables were log-transformed prior to parametric tests or analyzed by Wilcoxon signed ranks test. Ordinal variables were compared by Pearson chi square test. Significance was accepted at the 0.05-level for all statistical analyses. No systematic sample size calculation was performed by virtue of the pilot character of the study.

RESULTS

Participant characteristics and disease activity

Control participants were significantly taller and heavier than their patient fellow, although BMI was similar between groups (table 1). There was no difference between patients and controls in terms of age, employment status, smoking behavior or self-reported level of endurance- and strength exercise. Patients included in the study presented with a mean disease symptom duration of 15.5 ±6.6 years. Regarding diagnosis, six patients had AS, one had PsA, and the remaining three presented with axial SpA. One patient had previously undergone prosthetic replacement of the left hip due to congenital causes, and measures of muscle function and QF volume and CSA from his left leg were therefore excluded from all comparative analyses.

Body composition

There was no significant difference in bone mineral density (BMD) or BMD *T*-score between patients and their respective controls (Table 2). Regarding muscle mass, there was no difference in total LBM. Appendicular lean mass (RSMI) was however significantly lower in the patient group (p=0.02) (Table 2). Both groups displayed a wide range of FM, and there was no significant difference in total body fat %, android fat % or gynoid fat % (Table 2).

QF volume and CSA

Within-group paired samples correlations of total QF volume, mean and maximal CSA measures of the right and left leg was very strong and significant for both patients (range: r= 0.92-0.97, n= 9, Pat 01 excluded) and controls (range: r= 0.98-0.99, n= 10) (see appendix). Total QF volume of the right and left leg was significantly higher in control participants (Table 3). Mean QF CSA right leg was similar between groups and the moderate difference in mean QF CSA left leg was also non-significant (Table 3). We observed a trend towards lower maximal QF CSA in the right leg (p=0.14) and left leg (p=0.06) in the patients (Table 3).

Muscle function

Statistical evaluation of within-group paired samples correlation presented a non-significant, moderate positive relationship between measures of RFD right and left leg for both patients (r= 0.45, n= 9, Pat 01 excluded) and controls (τ= 0.33) (see appendix). Regarding other variables of muscle function, correlation with data from the contralateral leg was very strong

for patients (range: r= 0.85-0.94, n= 10) and controls (range: r= 0.78-0.95) (see appendix). Between-group analyses of muscle function revealed no significant difference in RFD (Table 3). The SpA patients had significantly lower values for MVC torque left leg (175 ±42 Nm, Pat 01 omitted) compared to the controls (223 ±32 Nm, Ctr 01 omitted) (p= 0.01, CI:-80.9;-14.4), with a similar trend for the right leg (201 ±35 Nm vs. 227 ±26 Nm, p= 0.08, CI:-57.0;4.1) (Figure 1). There was no significant difference in measures of specific strength when force was normalized to total QF volume and maximal QF CSA on the right leg (Table 3). Muscle strength normalized to QF maximal CSA left leg was significantly lower in the SpA patients (p=0.04), with a complementary trend detected for muscle force normalized to total left QF volume (p=0.12) (Table 3). Regarding muscle endurance, the number of repetitions at 30% MVC was practically identical (Table 3). There was a significant group difference in total workload right leg and a corresponding trend for the left leg (Table 3).

Muscle morphology

Mean ±SD number of muscle fibers attained and measured was 578 ±211 and 536 ±183 for patients and controls respectively (p= 0.65, CI: -159.9;243.7).

Fiber type distribution and fiber CSA

Muscle fiber type distribution was similar between patients and controls, although the individual variation was large in both groups (Table 4). Mean type 1 fiber CSA was similar between patients (mean ±SD 5269 ±1890 μm^2) and controls (5598 ±1355 μm^2) (p= 0.54, CI: -1502.3;884.3), whereas mean fiber CSA of type 2 fibers was 24.7% larger in controls (7019 ±1585 μm^2) compared to patients (5474 ±1840 μm^2) (p= 0.04, CI: -3281.0;-83.2) (Figure 2). Ratio of mean type 2 and type 1 fiber CSA was significantly higher in controls (Table 4).

Myonuclei and satellite cells

Mean number of myonuclei and central nuclei was comparable between groups (Table 4). There was no group difference in satellite cells pr. type 1 fibers, whereas the tending difference in satellite cells for type 2 fibers was non-significant (Table 4). Compared to controls, patients presented with a similar myonucelar domain for type 1 fibers (1469 ±240 μm^2 vs. 1478 ±189 μm^2, p= 0.93, CI: -244.7;226.1), and a non-significant tendency for lower type 2 fiber myonucelar domain (1351 ±243 μm^2 vs. 1512 ±239 μm^2, p= 0.15, CI: -392.6;70.2) (Figure 3).

CD66b and CD68 positive cells

The amount of CD66b (marker for neutrophils) positive cells per 100 muscle fibers was similar (2.8 ± 2.1 and 1.7 ±0.9 for patients and controls respectively) and test of log-transformed variables was non-significant (p= 0.51, CI:-0.65;1.21) (Figure 5). There was a tendency for increased level of CD68 (marker for macrophages) positive cells in patients (10.6 ±3.9 per 100 fibers) compared to controls (7.9±1.8), but the difference was non-significant (p= 0.11, non-parametric test) (Figure 4).

TABLES

Table 1. Subject characteristics*

Variable	Patients *n*=10	Controls *n*=10	*P* (95% CI lower; upper)^
Age (as of 31.12.14)	39 ±4.1 (33-44)	38 ±5.1 (31-45)	0.57(-3.7;6.3)
Body height (cm)	178.1 ±6.4 (169.5-190.5)	181.8 ±6.3 (174.5-190.5)	0.04 (-7.3;-0.2)
Femur length	42.4 ±2.4 (39.5-46.4)	45.4 ±2.4 (42.5-49.5)	0.002 (-4.7;-1.4)
Femur length/Body height (%)	24 ±1 (23-25)	25 ±1 (23-27)	0.01 (-0.02;-0.004)
Body mass (kg)	75.2 ±7.8 (65.0-90.6)	79.9 ±11.4 (74.2-95.5)	0.04 (-9.0;-0.3)
BMI, kg/m^2	23.6 ±1.3 (21.9-25.6)	24.0 ±2.3 (20.0-27.8)	0.43 (-1.6;0.7)
Smoking behavior			0.35§
Non-smoker, n (%)	8 (80)	7 (70)	
Previous smoker, n (%)	1 (10)	3 (30)	
Current smoker, n (%)	1 (10)	0 (0)	
Full-time employment, n (%)	10 (100)	10 (100)	1.00
Level of endurance exercise (1-4)	2.3 ±0.7 (1-3)	2.2 ±0.6 (1-3)	0.89§
Level of strength exercise (1-4)	1.8 ± 0.6 (1-3)	2.0 ±0.7 (1-3)	0.77§
Diagnosis			
AS, n (%)	6 (60)		-
Axial SpA, n (%)	3 (30)		-
PsA, n (%)	1 (10)		-
HLA-B27 positive, n (%)	9 (90)		-
Time since diagnosis, years	10.0 ±7.9 (1-28)		-
Duration of symptoms, years	15.5 ± 6.6 (7-29)		-
BASDAI score	2.7 ±1.1 (0-3.7)		-
BASFI score	0.9 ±0.8 (0-2.6)		-
BASMI score	2.3 ±1.1 (0.7-4.6)		-
CRP	7.0 ±7.7 (<1-21)		-
ESR	9.3 ±9.7 (<1-26)		-
Anti-inflammatory medication			
NSAIDs, n (%)	6 (60)	0 (0)	-
DMARDs, n (%)	2 (20)	0 (0)	-
TNF-inhibitors, n (%)	4 (40)	0 (0)	-

*Values are mean ±SD (range) unless otherwise indicated. ^Comparison between patients and controls tested by paired samples t-test unless otherwise indicated. §: Pearson Chi Square test. AS: Ankylosing Spondylitis. BASDAI: Bath AS Disease Activity Index. BASFI: Bath AS Functional Index. BASMI: Bath AS Metrology Index. BMI: Body mass index. CI: Confidence Interval. CRP: C-reactive protein. DMARDs: Disease modifying anti-rheumatic drugs. ESR: Erythrocyte sedimentation rate. NSAIDS: Non-steroidal anti-inflammatory drugs. PsA: Psoriasis arthritis. SpA: Spondyloarthritis. TNF: Tumor Necrosis Factor.

Table 2. Body composition analysis*

Variable	Patients *n*=10	Controls *n*=10	*P* (95% CI lower; upper)^
BMD, g/cm^2	1.27 ±0.04 (1.20-1.33)	1.31 ±0.13 (1.11-1.60)	0.39 (-0.15;0.06)
BMD, *T*-score	0.65 ±0.43 (0-1.3)	1.09 ±1.33 (-0.9-4.0)	0.37 (-1.5;0.6)
Lean body mass, kg/m^2	18.2 ±1.8 (15.1-21.3)	18.6 ±1.6 (17.1-21.6)	0.32 (-1.2;0.4)
Appendicular lean mass;			
RSMI, kg/m^2	8.3 ±0.9 (7.2-9.6)	8.8 ±0.8 (8.0-10.1)	0.02 (-0.9;-0.1)
Body fat, %	21.9 ±7.0 (8.4-30.2)	20.1 ±6.2 (12.6-31.2)	0.47 (-3.5;7.1)
Android fat, %	25.3 ±10.9 (6.3-39.7)	21.6 ±10.1 (10.6-36.5)	0.31 (-4.1;11.3)
Gynoid fat, %	21.0 ±6.9 (8.2-29.6)	20.8 ±5.7 (15.0-32.8)	0.95 (-5.3;5.6)

*Values are mean ±SD (range) unless otherwise indicated. ^Comparison between groups tested by paired samples t-test unless otherwise indicated. §: Wilcoxon signed ranks test. BMD: Bone mineral density. CI: Confidence Interval. RSMI: Relative skeletal muscle index.

Table 3. Quadriceps femoris – parameters of volume, CSA and muscle function*

Variable	Patients *n*=10(#:*n*=9)	Controls *n*=10 (#: *n*=9)	*P* (95% CI lower; upper)^
QF total volume			
Right leg, cm^2	2093 ±361 (1501-2676)	2316 ±268 (1879-2718)	0.01 (-386.7;-59.7)
Left leg, cm^2#	1977 ±415 (1413-2708)	2278 ±304 (1793-2691)	0.01 (-489.2;-112.6)
QF mean CSA			
Right leg, cm^2	62 ±9 (48-76)	64 ±7 (53-72)	0.42 (-6.5;3.0)
Left leg, cm^2#	58 ±10 (45-74)	62 ±8 (51-72)	0.17 (-10.2;2.2)
QF max CSA			
Right leg, cm^2	84±10 (66-100)	88±9 (75-105)	0.14 (-9.7;1.6)
Left leg, cm^2#	79 ±12 (63-95)	86 ±10 (72-104)	0.06 (-14.3;0.3)
Specific strength			
MVC Nm/QF total vol., right leg, Nm/cm^3	0.097 ±0.01 (0.08-0.12)	0.098 ±0.01 (0.09-0.11)	0.79 (-0.01;0.01)
MVC Nm/QF total vol., left leg, Nm/cm^3#	0.090 ±0.01 (0.07-0.11)	0.098 ±0.01 (0.09-0.11)	0.12 (-0.02;0.00)
MVC Nm/QF max CSA, right leg, Nm/cm^2	2.41 ±0.37 (1.92-3.04)	2.60 ±0.25 (2.22-2.97)	0.20 (-0.50;0.12)
MVC Nm/QF max CSA, left leg, Nm/cm^2#	2.22 ±0.37 (1.75-2.82)	2.60 ±0.24 (2.26-2.99)	0.04 (-0.74;-0.02)
RFD			
Right leg, Nm/10 ms	1716 ±447 (1095-2577)	1873 ±937 (769-3632)	0.95 (-0.44;0.42)£
Left leg, Nm/10 ms#	1621 ±314 (1274-2273)	1949 ±889 (1187-4194)	0.24 (-0.38;0.11)£
Muscle endurance			
Number of repetitions, right leg	35.4 ±14.3 (15-53)	37.9 ±6.2 (29-50)	0.63 (-13.8;8.8)
Number of repetitions, left leg#	40.0 ±13.4 (23-60)	39.1 ±10.4 (26-57)	0.89 (-13.5;15.3)
Total workload (reps x kg), right leg, kg	556.6 ±206.8 (248.7-809.2)	680.8 ±133.2 (479.2-946.4)	0.05 (-246.7;-1.7)
Total workload (reps x kg), left leg, kg#	563.7 ±217.0 (287.0-946.1)	685.8 ±177.4 (427.6-1029.6)	0.14 (-295.1;51.0)

*Values are mean ±SD (range) unless otherwise indicated. #: *N*= 9 patients, 9 controls. Excludes pair 1 due to prosthesis left hip Pat 01. ^: Comparison between groups tested by paired samples t-test unless otherwise

indicated. £: Log-transformed variable, paired samples t-test. CSA: Cross-sectional area. MVC: Maximal voluntary contraction. Nm: Newtonmeter. QF: Mm. quadriceps femoris. RFD: Rate of force development.

Table 4. Muscle morphology – parameters obtained from biopsy of *m. vastus lateralis***

Variable	**Patients** ***n*=10**	**Controls** ***n*=10**	***P*(95% CI lower; upper)^**
Muscle fiber distribution			
Type 1, %	54.9 ±13.8 (33.6-76.8)	48.5 ±11.4 (30.5-68.3)	0.32 (-7.5;20.5)
Type 2, %	45.1 ±13.8 (23.2-66.4)	51.5 ±11.4 (31.7-69.5)	0.34 (-4.2;10.8)
Ratio CSA type 2/ type 1	1.05 ±0.17 (0.83-1.37)	1.27 ±0.22 (0.95-1.94)	0.05 (-0.442;-0.002)
Myonuclei			
Type 1, pr. fiber	3.6 ±1.1 (2.2-6.0)	3.8 ±0.6 (3.1-4.8)	0.65 (-0.96;0.63)
Type 2, pr. fiber	4.0 ±1.1 (2.6-6.0)	4.6 ±1.0 (3.2-6.5)	0.25 (-1.75;0.51)
Central nuclei			
Type 1, pr. fiber	0.02 ±0.03 (0.00-0.10)	0.08 ±0.14 (0.00-0.44)	0.20§
Type 2, pr. fiber	0.03 ±0.03 (0.00-0.08)	0.08 ±0.11 (0.00-0.32)	0.26§
Satellite cells, Pax7-positive			
Type 1, pr. 100 fibres	8.8 ±8.0 (1.5-29.7)	6.4 ±4.2 (1.6-17.1)	0.62 (-0.61;0.97)£
Type 2, pr. 100 fibres	5.5 ±2.7 (2.6-11.3)	8.0 ±6.0 (3.4-24.3)	0.13 (-0.76:0.12)£

*Values are mean ±SD (range) unless otherwise indicated. §: Wilcoxon signed ranks test. £: Log-transformed variable, paired samples t-test. CD68: marker for macrophages. CD66b: marker for neutrophils. CSA: Cross-sectional area. ECM: Extracellular matrix.

FIGURES

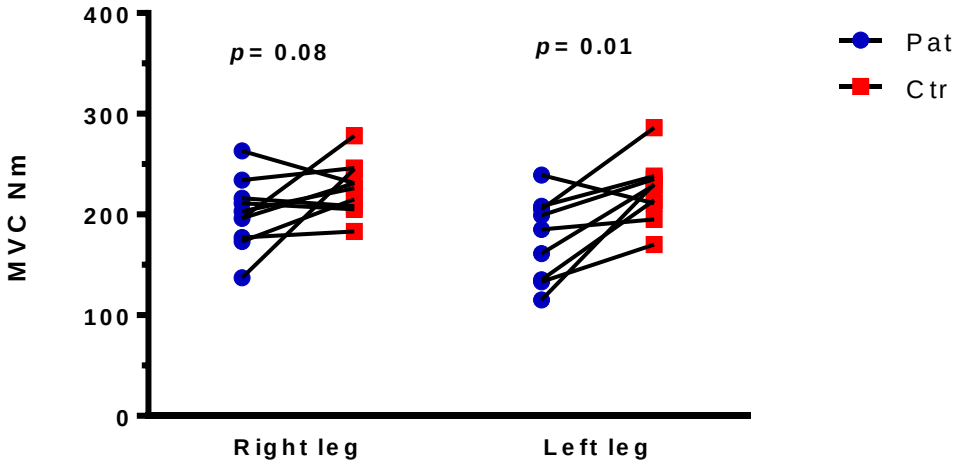

Figure 1. Maximal voluntary contraction (MVC) torque measured as isometric contraction of m. quadriceps femoris. Lines drawn signify the pairwise match of patient-control.

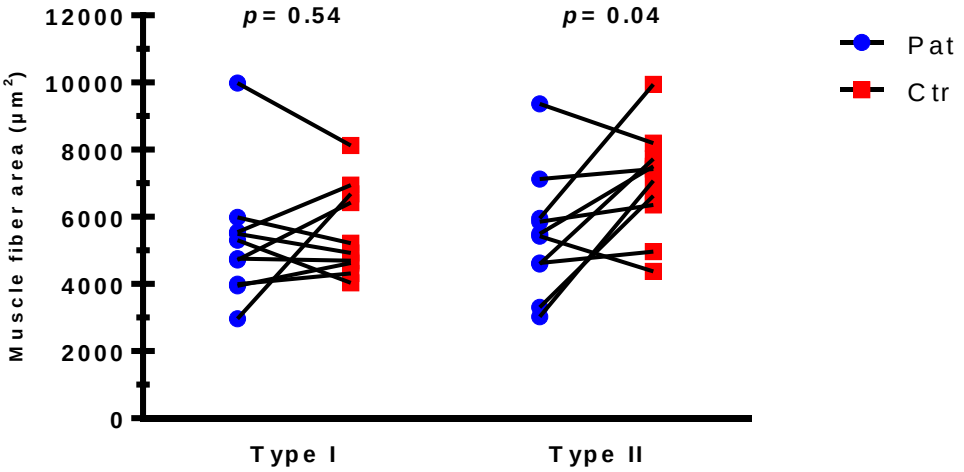

Figure 2. Muscle fiber CSA for type 1 and type 2 fibers. Lines drawn signify the pairwise match of patient-control.

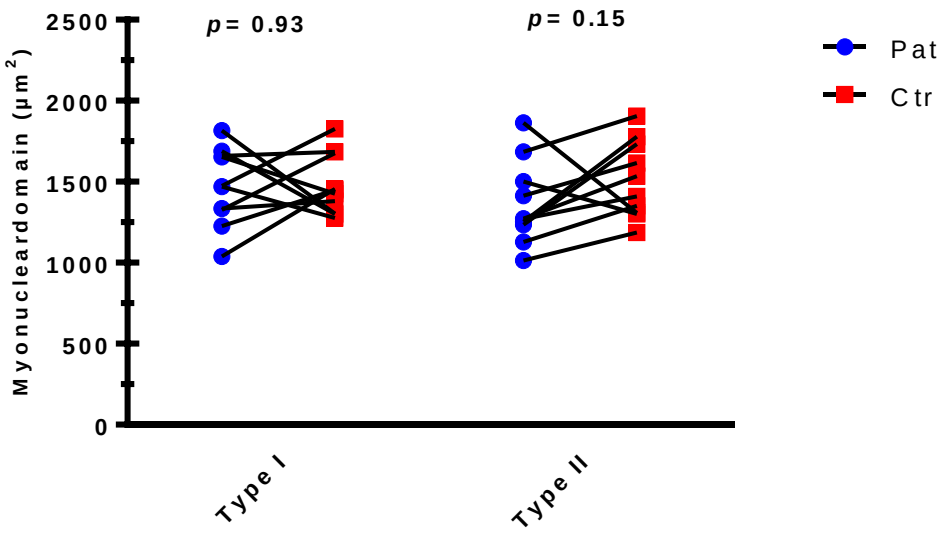

Figure 3. Myonuclear domain for muscle fiber type 1 and type 2. Lines drawn signify the pairwise match of patient-control.

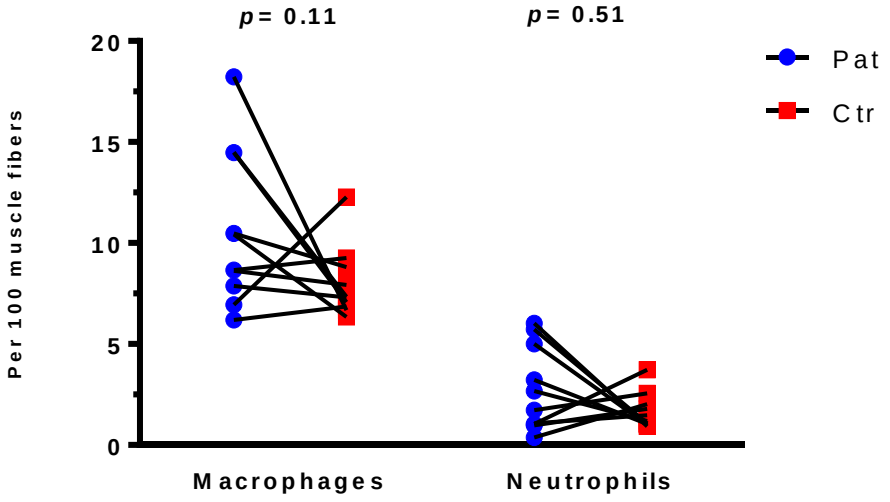

Figure 4. Number of CD68 positive macrophages and CD66b positive neutrophils in ECM. Lines drawn signify the pairwise match of patient-control – some lines appear duplicated as they represent pairs with similar values.

DISCUSSION

The main findings of the present study were a significant lower appendicular LBM and muscle fiber type 2 CSA, as well as a tendency towards inferior muscle strength in SpA patients compared to healthy controls. Furthermore, in the muscle biopsies of SpA patients, we detected a moderate trend towards increased frequency of macrophages, heterogeneous leukocytes that can both stimulate and attenuate muscle tissue repair (46).

Our observation of significantly lower appendicular LBM and no difference in total FM in SpA patients concur with the results of two previous studies (19, 22) , but oppose no difference in body composition reported elsewhere (23-26). Sari et al. (21) detected lower FM in male AS patients compared to healthy controls, although body composition was estimated by methods of lower accuracy (47). In the current study, one patient presented with extremely low adipose tissue values when compared to both reference data (48) and the other patients, thus potentially influencing between-group analyses of FM. Comparison of body composition values between studies is challenging as most studies investigating SpA patients and healthy controls examine absolute values of FM and LBM (kg), bypassing body composition values relative to stature (kg/m^2) despite group differences in height and/or mass (19, 23, 25). Furthermore, our study inclusion criteria did not impose any restrictions on exercise habits amongst the participants, whereas some of the studies cited admitted only sedentary participants or did not account for level of PA. In this study both patients and controls presented with appendicular LBM values that correspond to median reference data for white males of the same age group, but the observed FM % was lower than median reference values (48).

We observed lower appendicular LBM in concert with a trend towards inferior muscle strength in the SpA patients. Direct comparison of muscle strength variables to other studies reporting analogous lower muscular force in AS patients (17-19) is challenging due to variation in measurement values, contraction type and muscle group studied. Previous studies have not matched patients and controls for level of PA (17-19), and the observed group difference may have been confounded by disparity in training status. In this study, patients were matched with a fellow control reporting corresponding levels of exercise as well as type of exercise. Nonetheless, we observed a significantly lower left knee extensor peak torque in the SpA patients, with a similar trend for the right leg. In contrast, a recent study (49) reported

no difference in isometric knee extensor strength between AS patients and healthy controls with similar levels of PA, as well as comparable levels of muscle force values when normalized to ultrasound-derived measures of QF anatomical CSA (specific strength). Along with total muscle volume, anatomical CSA is considered a strong predictor of muscle force (50). In the present study, the significantly larger total QF volume in control participants (Table 3) may be accounted for by the coincidental inferior femur length/body height ratio in patients (Table 1). Upon normalizing muscle force to QF maximal CSA (specific strength), the tending group difference in muscle force for the right leg was diminished (Table 3). Left leg muscle strength normalized to QF maximal CSA was however still significantly lower (p= 0.04) (Table 3) in patients, indicating a possible difference in muscle quality.

In contrast to other reports (17, 18, 51), we observed similar levels of relative muscle endurance in patients and controls. The difference in total workload can be attributed to group diversity in muscle strength, and the number of repetitions at 30% MVC was similar between patients and controls (Table 3). Muscle endurance capacity is partially dependent on the expression of MHC isoforms (52), although a strong correlation to capillary density has also been suggested (53). We did not assess capillary density, but propose that comparable levels of muscle endurance portray the group similarity in muscle fiber composition.

An important observation in the current study is the significantly smaller type 2 fibers in the patient population. Myofiber size is positively correlated to muscle strength (54, 55), and lower type 2 fiber CSA in SpA patients may explain the concomitant decreased muscle strength. Fiber hypertrophy is further reported to enhance maximal torque and rate of torque development (55, 56) and measures of MVC and RFD are considered to be highly related (57). The observation of no significant group difference in RFD despite lower maximum strength in the SpA patients was therefore surprising. However, our RFD data shows large variance, and combined with a small sample size, measures of RFD may have been inflicted by a type 2 error.

Previous studies have detected abnormalities in muscle biopsies yielded from AS patients, with case series observations of angulated and atrophic muscle fibers (16, 27, 28). However, myofiber CSA values and adequate matching to healthy controls are lacking in these studies, rendering it impossible to compare fiber size and study population to our current research. Disease manifestations may also differ from what we encounter in our present-day clinical

practice due to modern therapeutic options. To our knowledge, ours is the first present-day study assessing muscle morphology in SpA. A contemporary publication (58) explored the effect of chronic inflammation on muscle characteristics by comparing biopsies from patients with rheumatoid arthritis (RA) and patients with osteoarthritis (OA). They observed no difference in ratio of type 2/type 1 fiber CSA, contrary to the significant difference identified in our cohort. Strength training can induce preferential hypertrophy of type 2 fibers, whereas endurance exercise has limited effect on fiber size (59-61). We attempted to eliminate the influence of strength training volume on type 2 fiber size by matching patients and controls on self-reported exercise habits. Increased fiber CSA is associated with an initial enhancement in the ratio of myonuclei to cell cytoplasm volume (62), consistent with the observed trend towards greater type 2 fiber myonucelar domain in our control participants (figure 3). Furthermore, the non-significant, but slightly higher number of myonuclei in biopsies from controls (table 4) demonstrate the strong dependency between fiber hypertrophy and addition of new myonuclei (54, 60). On an opposite note, recent studies have highlighted the possibility that muscle atrophy is not accompanied by loss of myonuclei (63, 64). Although highly speculative, the trend towards decreased myonuclear domain in type 2 fibers from SpA patients may illustrate the effect of catabolic pathways on previously enlarged muscle fibers.

Satellite cells are important for skeletal muscle regeneration and for muscle hypertrophy in response to strength training (60). While enhanced number of satellite cells has been observed following strength training (54, 65, 66), pro-inflammatory pathways are associated with a decrease in volume and function of the satellite cell pool (12, 67). Interestingly, we observed a lower proportion of satellite cells in type 2 fibers in patients compared to controls. Although the group difference was non-significant ($p = 0.13$) (Table 4), we ponder on the possibility that inferior levels of satellite cells may curb the regenerative and/or adaptive ability of skeletal muscle in SpA patients. Noteworthy, no difference in satellite cell entity was observed between RA and OA patients (58), and no group difference was detected in *in vitro* satellite cell regenerative capacity (68), although this analysis was performed on a relatively small sub-sample. As emphasized by the authors, low-grade inflammation in the OA patients may have diluted the studied variables.

The present study detected a wide range in numbers of ECM located macrophages, with a non-significant trend ($p=0.11$) towards higher amounts in the biopsies from SpA patients. Inflammatory processes in muscle tissue are commonly observed following altered use or

muscle injury, but may also be a consequence of autoimmune skeletal muscle disease (12, 69). Neutrophils are usually the front-runners in the basic inflammatory response, followed by the invasion of different macrophage phenotypes. In the current study, level of neutrophils was comparable between patient and control participants. Due to the exploratory nature of the present study, biopsy samples were not stained for various macrophage phenotypes and we cannot estimate the proportion of pro- and anti-inflammatory macrophages. Pro-inflammatory macrophages secrete TNF and cytokines that may blunt myofiber regeneration, whereas anti-inflammatory macrophages promote differentiation of myogenic precursor cells. Furthermore, animal models have linked high levels of insulin-like growth factor (IGF)-1, a hormone involved in hypertrophic pathways, with the anti-inflammatory macrophage phenotype (12, 70). Macrophages are scarce in untrained muscle in healthy subjects, and we advised study participants to refrain from exercise the last two days prior to biopsy sampling. However, since the volume of macrophages is reported to plateau several days post-exercise (70, 71), the 48- hour training ban may not have been sufficient to exclude exercise-driven release of macrophages. Nonetheless, the interesting trend towards higher level of ECM macrophages in the SpA patients may also be related to the disease in question.

We did not measure level of TNF or interleukins associated with inflammatory, rheumatic pathways, and can only speculate as to whether the presence of underlying disease has had an impact on fiber type 2 protein turnover in the SpA patients. Increased level of pro-inflammatory cytokines can curtail anabolic pathways (13) and inflate the activity of proteasomes (69, 72) with a prime catabolic effect on fast fibers (73). Conflicting results are reported regarding the influence of heat shock proteins (74-76) and reactive oxygen species (77-79) on muscle homeostasis in inflammatory rheumatic disease. Ancillary immunoblot analysis of muscle biopsies from this study can potentially identify whether the presence of SpA disease is associated with increased myogenic expression of factors known to curtail muscle hypertrophy or increase proteolysis .

Patients included in this study reported low physical burden of disease. Likewise, both self-assessed disease activity and serum inflammatory values indicate low current disease activity (80) compared to other studies with SpA patients (19, 21, 23, 24, 26, 81), although ESR and CRP presented with a wide range. However, patient self-report disclosed a history of disease flares in most patients. Although BMI was similar between groups, the control participants were significantly taller and heavier than the patients. A corresponding difference in height

has been observed in other SpA case-control studies (19, 20, 23, 26), often explained as increased kyphosis due to axial disease involvement. We did not observe such structural spinal changes in our patient group, and consider the difference in height a chance occurrence.

The choice of a cross-sectional design imposes vulnerability to potential confounders. In the present study, no controls used pharmaceuticals on a regular basis. All patients reported continuous medication, with six patients taking NSAIDs and four patients on TNF-blockers (adalimumab, infliximab or certolizumab). Conducting a study on SpA patients with discontinued medication could perhaps unravel the true effect of disease on muscle tissue, but involves inescapable ethical barriers. Furthermore, mere inclusion of patients with an on-demand need for medication would weaken the external validity, as the majority of patients require regular medication (82). NSAIDs are recommended as the first-line option for pharmaceutical treatment of axial SpA (7). This drug group acts by blocking cyclo-oxygenase, an enzyme upstream to prostaglandin; a hormone-like mediator that may be involved in stimulating anabolic pathways. Conflicting results are reported in a systematic review (83) summarizing the effects of NSAIDs on parameters related to muscle growth. The majority of human trials do not uncover adverse effects of occasional use of NSAIDs on post-exercise protein synthesis or muscle hypertrophy. Certain animal studies do however indicate the opposite (84, 85), and the consequence of longstanding use is unknown. Furthermore, evidence suggests NSAIDs may blunt satellite cell activity and thus potentially curtail the potential of muscle hypertrophy (13).

Regarding TNF, prospective research has investigated the effect of initiating anti-TNF medication on parameters of body composition and the results are conflicting. Studies on SpA and psoriasis patients report shifts in body mass, FM and/or LBM after commencing anti-TNF medication (86-89). Discrepant results are reported in studies that noted no significant effect of TNF-blockers on body composition in patients with rheumatoid arthritis (90, 91). A novel study on patients with Crohns disease indicate a potential improvement in QF muscle mass and QF muscle strength subsequent to initiation of the TNF-blocker infliximab (92). The study lacked a control group, but observed no parallel change in self-reported diet or PA. Notwithstanding, increased nutritional uptake following infliximab may have confounded the results. There is a lack of human studies that histologically assess the impact of TNF-blockers on local muscle tissue. However, in mice with a genetic defect similar to dystrophy and myopathy, subcutaneous injections of TNF-blocker etanercept impeded inflammatory and

degenerative histological changes (93), and low-dose infliximab was beneficial for muscle strength and muscle fibrosis (94).

In summary, the effect of pharmaceutics commonly used in SpA on muscle tissue is equivocal and we cannot discard a confounding effect on study variables. Sub-group analysis of medication in our patient cohort is conducted on a small sample and should be interpreted with caution. Compared to the NSAIDs group, patients on TNF-blockers presented with significantly lower ESR and CRP values (data not shown, see appendix). Additionally, we noted a moderate tendency towards lower BASDAI and BASFI in the TNF group, although low BASFI scores irrespective of medication suggest a floor effect (data not shown, see appendix). We further observed a trend for elevated maximal and specific strength in the NSAIDs subgroup, but no parallel divergence in muscle mass or myofiber size (data not shown, see appendix). Possibly related to medication, the difference in muscle strength may also reflect previous disease flares in the TNF subgroup that could have impeded their ability to engage in rigorous exercise. Collectively, our data may suggest a need for future SpA exercise studies to consider the potential effect of medication type on outcome variables.

There are several limitations to our study. Despite aiming to pairwise match patients and controls for level of endurance- and strength exercise, an undisclosed group difference in training volume could have influenced study variables. Although one patients and his fellow control reported no leisure time exercise, our study may have been subject to selection bias by predominantly recruiting participants at the higher level of PA spectrum. In support, measures of maximal isometric muscle force in our study are comparable and slightly superior to values obtained using similar methods in a group of recreationally active young men and women (50). Furthermore, mean myofiber CSA corresponds to normative morphology data for Norwegian males, a report that also indicated a stronger relationship between fiber CSA and type and intensity of exercise rather than the amount of time spent on PA (95). Notably, the present study admitted individual patients and controls presenting with a mean fiber size comparable to power-lifters (96).

All tests and analyses were performed by researchers that were not blinded. Although attempts were made to standardize all measurements, knowledge of group membership may have influenced the outcome variables. The limited number of participants may entail low statistical power, possibly inflating the chance of making type 2 errors. Certain variables

presented with discrete effect sizes between right and left leg, perhaps related to the dispersion of collected data. Because of the exploratory nature of the study, we have discussed group differences in muscle morphology that did not adhere to the *a priori* alpha-level of 0.05, and the observed trends need further investigation. Future studies with adequate statistical power are warranted to confirm our results and elucidate if catabolic pathways are up-regulated in SpA patients.

In conclusion, the present exploratory study indicates that the presence of SpA disease is associated with reduced appendicular LBM, muscle strength and type 2 fiber CSA. Physical therapists can therefore be advised to include progressive resistance training in their treatment interventions for SpA patients as a possible countermeasure against the observed negative effects on muscle tissue.

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Article Appendix

Table 1. Primary and secondary antibodies used during immunohistochemical staining.

	Catalog number	Manufacturer	Host	Dilutions
Primary antibodies				
Pax7	1 ea 13/14/13	DSHB	Mouse	1:100
SC71	1 11/8/12	DSHB	Mouse	1:100
CD68	M0718	Dako	Mouse	1:300
CD66b	CLB – B13.9	Saquin	Mouse	1:500
Laminin	Z0097	Dako	Rabbit	1:400
Dystrophin	Ab 15277	Abcam	Rabbit	1:500
Secondary antibodies				
Alexa flour 488	20010	Biotium	Goat antimouse	1:200
Alexa flour 594	20112	Biotium	Goat antirabbit	1:200

Supplementary statistical analyses:

Table 2. Patient participants within-group paired sampled correlations of parameters of QF volume and CSA (*Pat 01 excluded from analysis)*.

Variable		QF total volume left leg, cm^2	QF max CSA left leg, cm^2	QF mean CSA left leg, cm^2
QF total volume right leg, cm^2	Pearson's *r*	0.97		
	P (2-tailed)	<0.001		
	N	9		
QF max CSA right leg, cm^2	Pearson's *r*		0.92	
	P (2-tailed)		0.001	
	N		9	
QF mean CSA right leg, cm^2	Pearson's *r*			0.96
	P (2-tailed)			<0.001
	N			9

CSA: Cross-sectional area. QF: Mm. quadriceps femoris.

Table 3. Control participants within-group paired sampled correlations of parameters of QF volume and CSA.

Variable		QF total volume left leg, cm^2	QF max CSA left leg, cm^2	QF mean CSA left leg, cm^2
QF total volume right leg, cm^2	Pearson's *r*	0.99		
	P (2-tailed)	<0.001		
	N	10		
QF max CSA right leg, cm^2	Pearson's *r*		0.98	
	P (2-tailed)		<0.001	
	N		10	
QF mean CSA right leg, cm^2	Pearson's *r*			0.99
	P (2-tailed)			<0.001
	N			10

CSA: Cross-sectional area. QF: Mm. quadriceps femoris.

Table 4. Patient participants within-group paired sampled correlations of parameters of QF function (*Pat 01 excluded from analysis)*.

Variable		RFD left leg, Nm/10 ms	MVC left leg, Nm	Number of repetitions, left leg	Total workload (reps x kg) left leg, kg	MVC Nm/QF total vol., left leg, Nm/cm^3	MVC Nm/QF max CSA, left leg, Nm/cm^2
RFD right leg, Nm/10ms	Pearson's *r*	0.45					
	P (2-tailed)	0.23					
	N	9					
MVC right leg, Nm	Pearson's *r*		0.89				
	P (2-tailed)		0.001				
	N		9				
Number of repetitions, right leg	Pearson's *r*			0.94			
	P (2-tailed)			<0.001			
	N			9			
Total workload (reps x kg) right leg, kg	Pearson's *r*				0.85		
	P (2-tailed)				0.04		
	N				9		
MVC Nm/QF total vol., right leg, Nm/cm^3	Pearson's *r*					0.90	
	P (2-tailed)					0.001	
	N					9	
MVC Nm/QF max CSA, right leg, Nm/cm^2	Pearson's *r*						0.87
	P (2-tailed)						0.02
	N						9

CSA: Cross-sectional area. MVC: Maximal voluntary contraction. Nm: Newtonmeter. QF: Mm. quadriceps femoris. RFD: Rate of force development.

Table 5. Control participants within-group paired sampled correlations of parameters of QF function (*Pat 01 excluded from analysis)*.

Variable		RFD left leg, Nm/10 ms	MVC left leg, Nm	Number of repetitions, left leg	Total workload (reps x kg) left leg, kg	MVC Nm/QF total vol., left leg, Nm/cm^3	MVC Nm/QF max CSA, left leg, Nm/cm^2
RFD right leg, Nm/10ms	Kendall's τ	0.33					
	P (2-tailed)	0.18					
	N	10					
MVC right leg, Nm	Pearson's *r*		0.95				
	P (2-tailed)		<0.001				
	N		10				
Number of repetitions, right leg	Pearson's *r*			0.78			
	P (2-tailed)			0.007			
	N			10			
Total workload (reps x kg) right leg, kg	Pearson's *r*				0.84		
	P (2-tailed)				0.02		
	N				10		
MVC Nm/QF total vol., right leg, Nm/cm^3	Pearson's *r*					0.83	
	P (2-tailed)					0.003	
	N					10	
MVC Nm/QF max CSA, right leg, Nm/cm^2	Pearson's *r*						0.78
	P (2-tailed)						0.07
	N						10

CSA: Cross-sectional area. MVC: Maximal voluntary contraction. Nm: Newtonmeter. QF: Mm. quadriceps femoris. RFD: Rate of force development.

Table 6. Subject characteristics: NSAIDs vs TNF*

Variable	NSAIDs *n*= 6	TNF *n*= 4	*P* (95% CI lower; upper)^
Age (as of 31.12.14)	39 ±4.8	39 ±3.6	0.93 (-6.8;6.3)
BMI, kg/m^2	23.4 ±1.3	24.0 ±1.5	0.50 (-2.6;1.4)
Diagnosis			
AS, n	4	2	-
Axial SpA, n	2	1	-
PsA, n	0	1	-
HLA-B27 positive, n	5	4	-
Time since diagnosis, years	9.5 ±10.5	10.8 ±2.2	0.82 (-13.8;11.3)
Duration of symptoms, years	15.7 ±8.8	15.3 ±1.5	0.93 (-10.1;10.9)
BASDAI score	3.1 ±0.4	2.2 ±1.6	0.15 (-0.51;0.09)£
BASFI score	1.3 ±0.8	0.4 ±0.5	0.11 (-0.2;1.9)
BASMI score	2.2 ±1.4	2.6 ±0.7	0.61 (-2.2;1.4)
CRP	11.7 ±6.4	0.0 ±0.0	0.007 (4.1;19.2)
ESR	13.8 ±10.3	2.5 ±0.6	0.001 (1.0;2.6)£

Values are mean ±SD unless otherwise indicated. ^Comparison between patients on NSAIDs and TNF tested by independent samples t-test unless otherwise indicated. £: Log-transformed variable, independent samples t-test. AS: Ankylosing Spondylitis. BASDAI: Bath AS Disease Activity Index. BASFI: Bath AS Functional Index. BASMI: Bath AS Metrology Index BMI: Body mass index. CI: Confidence Interval. CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate. NSAIDS: Non-steroidal anti-inflammatory drugs. TNF: Tumor Necrosis Factor. SpA: Spondyloarthritis. PsA: Psoriasis arthritis

Table 7. Body composition analysis: NSAIDs vs TNF*

Variable	NSAIDs *n*=6	TNF *n*= 4	*P* (95% CI lower; upper)^
BMD, g/cm^2	1.27 ±0.05	1.27 ±0.05	0.94 (-0.07;0.07)
BMD, *T*-score	0.63 ±0.47	0.68 ±0.43	0.89 (-0.72;0.63)
Lean mass, kg/m^2	17.9 ±2.4	18.5 0.45	0.58 (-3.1;1.9)&
Appendicular lean mass; RSMI, kg/m^2	8.4 ±1.0	8.2 ±0.8	0.76 (-3.4;2.2)
Body fat, %	20.8 ±9.1	23.6 ±1.9	0.49 (-12.3;6.7)&
Android fat, %	23.7 ±13.6	27.6 ±5.8	0.60 (-20.8;12.9)
Gynoid fat, %	20.2 ±8.7	22.2 ±3.4	0.67 (-12.8;8.7)

*Values are mean ±SD unless otherwise indicated. ^Comparison between groups tested by independent samples t-test unless otherwise indicated. &: Equal variance not assumed. BMD: Bone mineral density. CI: Confidence Interval. RSMI: Relative skeletal muscle index.

Table 8. QF – parameters of volume, CSA and muscle function: NSADIs vs TNF*

Variable	NSAIDs *n*=6(#*n*=5)	TNF *n*=4	*P* (95% CI lower; upper)^
MVC right leg, Nm	217 ±29	175 ±28	0.053 (-0.6;84.4)
MVC left leg, Nm#	193 ±39	154 ±39	0.18 (-23;101)
QF total volume			
Right leg, cm^2	2163 ±441	1987 ±203	0.48 (-375;727)
Left leg, cm^2#	2039 ±495	1899 ±345	0.65 (-553;832)
QF mean CSA			
Right leg, cm^2	64 ±11	59 ±4	0.44 (-9;19)
Left leg, cm^2#	60 ±12	57 ±8	0.65 (-14;21)
QF max CSA			
Right leg, cm^2	85 ±13	82 ±8	0.71 (-14;19)
Left leg, cm^2#	80 ±14	77 ±12	0.71 (-17;24)
Specific strength			
MVC Nm/QF total vol., right leg, Nm/cm^3	0.10 ±0.02	0.09 ±0.01	0.14 (-0.01;0.03)
MVC Nm/QF total vol., left leg, Nm/cm^3#	0.10 ±0.01	0.08 ±0.01	0.08 (-0.0;0.03)
MVC Nm/QF max CSA, right leg, Nm/cm^2	2.6 ±0.34	2.1 ±0.21	0.04 (0.01;0.90)
MVC Nm/QF max CSA, left leg, Nm/cm^2#	2.4 ±0.36	2.0 ±0.23	0.08 (-0.07;0.92)
RFD			
Right leg, Nm/10 ms	1869 ±451	1486 ±376	0.20 (-249;1015)
Left leg, Nm/10 ms#	1611 ±408	1632 ±204	0.93 (-553;512)
Muscle endurance			
Number of repetitions, right leg	31 ±13	42 ±15	0.26 (-32;10)
Number of repetitions, left leg#	35 ±11	46 ±15	0.28 (-31;10)
Total workload (reps x kg), right leg, kg	537 ±224	586 ±206	0.73 (-373;275)
Total workload (reps x kg), left leg, kg#	548 ±169	583 ±294	0.83 (-401;332)

*Values are mean ±SD unless otherwise indicated. #: *N*= 5 patients, Pat 01 excluded due to prosthesis left hip. ^: Comparison between groups tested by independent samples t-test unless otherwise indicated. £: Log-transformed variable, independent samples t-test. CSA: Cross-sectional area. MVC: Maximal voluntary contraction. Nm: Newtonmeter. QF: Mm. quadriceps femoris. RFD: Rate of force development.

Table 9. Muscle morphology – parameters obtained from biopsy of *m. vastus lateralis:* NSAIDs vs TNF*

Variable	NSAIDs *n*=6	TNF *n*=4	*P*(95% CI lower; upper)^
Muscle fiber distribution			
Type 1, %	52 ±14	59 ±14	0.45 (-0.28;0.14)
Muscle fibre CSA			
Type 1, μm^2	5483 ±2443	4948 ±730	0.87 (-0.47;0.54)£
Type 2, μm^2	5692 ±2241	5149 ±1248	0.67 (-2328;3414)
Ratio CSA type 2/ type 1	1.06 ±0.19	1.03 ±0.17	0.81 (-0.24;0.30)
Myonuclei			
Type 1, pr. fiber	3.7 ±1.3	3.5 ±1.0	0.83 (-1.6;1.9)
Type 2, pr. fiber	4.3 ±1.2	3.7 ±1.0	0.46 (-1.1;2.3)
Myonuclear domain			
Type 1, μm^2	1475 ±253	1460 ±258	0.93 (-364;394)
Type 2, μm^2	1308 ±216	1415 ±299	0.53 (-480;266)
Central nuclei			
Type 1, pr. fiber	0.03 ±0.03	0.01 ±0.01	0.17§
Type 2, pr. fiber	0.03 ±0.03	0.02 ±0.02	0.57 (-480;266)
Satellite cells, Pax7-positive			
Type 1, pr. 100 fibres	6.6 ±3.9	11.9 ±11.9	0.38 (-1.71;0.72)£
Type 2, pr. 100 fibres	6.3 ±3.0	4.2 ±1.9	0.24 (-1.7;6.0)
CD68 ECM, pr. 100 fibres	10.5 ±3.3	10.9 ±5.2	0.89 (-6.5;5.7)
CD66b ECM, pr. 100 fibres	3.3 ±2.5	2.0 ±1.3	0.37 (-1.9;4.5)

*Values are mean ±SD unless otherwise indicated. §: Mann-Whitney U test. CD68: marker for macrophages. CD66b: marker for neutrophils. CSA: Cross-sectional area. ECM: Extracellular matrix. £: Log-transformed variable, independent samples t-test.

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2) Informed consent form (patients)
3) Informed consent form (controls)
4) Questionnaire including BASDAI and BASFI (patients)
5) Questionnaire (controls)
6) BASMI
7) Information on muscle biopsy wound care (Stell av sår etter muskelbiopsi)

Att. 1: *Approval from Regional Ethics Committee*

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anette Solli Karlsen	22845522	04.09.2014	2014/893/REK sør-øst
				A
			Deres dato:	Deres referanse:
			25.08.2014	

Vår referanse må oppgis ved alle henvendelser

Hanne Dagfinrud

Norges Idrettshøgskole, Diakonhjemmet Sykehus

2014/893 Har pasienter med spondyloartritt endringer i muskelvev og muskelfunksjon som følge av sin inflammatoriske revmatiske sykdom?

Forskningsansvarlig: Norges Idrettshøgskole, Diakonhjemmet Sykehus **Prosjektleder:** Hanne Dagfinrud

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av

Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet

12.06.2014. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektbeskrivelse

Formålet med studien er å undersøke muskelstyrke og karakteristika ved muskelvev hos pasienter med spondyloartritt sammenlignet med friske kontroller.

Spondyloartritt er en revmatisk inflammatorisk sykdom som rammer personer i ung alder. Tidligere studier har indikert at denne pasientgruppen har redusert muskelstyrke og utholdenhet sammenlignet med friske personer i samme alder.

Det planlegges å inkludere 10 pasienter mellom 30 og 35 år med spondyloartritt fra Revmatologisk avdeling ved Diakonhjemmet Sykehus. I prosjektet skal det innhentes selvrapporterte data om medikamentbruk, sykdomsspesifikke bakgrunnsdata og sykdomsaktivitet samt fysisk funksjon. Det skal tas blodprøver og muskelbiopsi fra m. quadriceps femoris (rett lårmuskel).

Muskelfunksjon skal måles isometrisk ved maksimal kraft og hastighet på kraftutmåling, samt ved en utholdenhetstest, disse undersøkelsene skal utføres under instruksjon av fysioterapeut. I tillegg skal muskelmasse måles ved Dual-energy X-ray absorptiometry (DXA) samt målinger av tverrsnittsareal og –volum av m. quadriceps femoris ved MR.

Det primære endepunktet er størrelse av muskelfibre målt ved tverrsnittsareal på type I og II muskelfibre. Sekundære endepunkter er inflammasjon i muskelvev og forekomst av regulatorer av muskelfiberstørrelse målt ved hhv inflammatoriske celler og cytokiner, og proteiner som er involvert i muskelnedbryting.

Resultater skal sammenlignes med foreliggende referansemateriale ved Norges Idrettshøyskole fra friske personer.

Biologisk materiale skal inngå i ny spesifikk forskningsbiobank, «Muskelvev hos pasienter med spondyloartritt», med ansvarshavende Truls Raastad ved Norsk Idrettshøyskole.

Saksbehandling

Prosjektet ble behandlet i møte 12.06.2014, og det ble fattet et utsettende vedtak.

Komiteen ba om tilbakemelding på følgende merknader:

Det forutsettes at biologisk materiale oppbevares i kun 5 år etter prosjektslutt, jf.helseforskningsloven § 38. Det bes om at formuleringen «…og du må ha høy grad av sykdomsaktivitet» i informasjonsskrivet revideres eller strykes. Det bes om en redegjørelse for hvilke friske personer som skal utgjøre kontrollgruppen samt hva disse har samtykket til.

Søker har nå sendt tilbakemelding, denne ble mottatt 25.08.2014.

Det fremkommer av tilbakemelding at oppbevaringstiden for biologisk materiale er endret til 5 år, mot tidligere 15 år. Videre er informasjonsskrivet endret etter komiteens merknader.

Det fremkommer også at kontrollgruppen skal rekrutteres blant friske voksne spesifikt til dette prosjektet. Det er utarbeidet et separat informasjonsskriv til disse.

Ny vurdering

Komiteens leder har vurdert tilbakemeldingen, og denne er å anse som tilfredsstillende i forhold til komiteens merknader.

Vedtak

Prosjektet godkjennes med hjemmel i helseforskningsloven §§ 9 og 33.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Godkjenningen gjelder til 01.06.2015.

Komiteen godkjenner opprettelse av en spesifikk forskningsbiobank, "Muskelvev hos pasienter med spondyloartritt", med ansvarshavende Truls Raastad ved Norges Idrettshøyskole, med samme varighet som prosjektet. Biobankregisteret ved Nasjonalt Folkehelseinstitutt vil få kopi av dette brev.

Av dokumentasjonshensyn skal opplysninger og innsamlet biologisk materiale oppbevares i 5 år etter prosjektslutt. Opplysninger og materiale skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helseog omsorgssektoren».

Prosjektet skal sende sluttmelding på eget skjema, jf. helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK, jf. helseforskningsloven § 11.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf.helseforskningsloven § 10 tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal

Professor dr. med.

Leder

Anette Solli Karlsen

Komitesekretær

Kopi til:truls.raastad@nih.no; postmottak@diakonsyk.no; nina.hovland@fhi.no

Att. 2: *Informed consent form (patients)*

Forespørsel om deltakelse i forskningsprosjektet

"Har pasienter med spondyloartritt endringer i muskelvev og muskelfunksjon som følge av sin inflammatoriske revmatiske sykdom?"

Dette er et spørsmål til deg om å delta i en forskningsstudie for å undersøke muskelvev og muskelfunksjon hos pasienter med spondyloartritt (SpA). Vi ber om din deltakelse i prosjektet, så fremt du oppfyller kriteriene: Du må ha en spondyloartritt diagnose som er bekreftet av en revmatolog, du må ha hatt symptomer i minst fem år. I tillegg må du være mann i alderen 30-45 år, du må ha en kroppsmasseindeks på mellom 18.5-30, og snakke norsk eller engelsk. Du kan ikke ha eller tidligere ha hatt artritt i hofter eller knær, muskelsykdommer og ellers ha hatt skader i ben eller føtter i løpet av de 12 siste mnd. Du kan heller ikke delta dersom du tar medikamenter som inneholder kortikosterioder eller dersom du er allergisk mot lokalbedøvelse (tilsvarende det man får hos tannlegen).

Bakgrunn og hensikt
Tidligere studier har vist at pasienter med spondyloartritt har redusert muskelmasse, muskelstyrke og utholdenhet sammenlignet med friske kontroller. I tillegg er det vist patologiske endringer i muskulaturen tett til virvelsøylen. Imidlertid er konsekvensene av sykdommen på den øvrige skjelett-muskulaturen ukjent, det er kun en 30 år gammel liten studie som har undersøkt dette. I tillegg er det uklart om redusert muskelstyrke og muskelkvalitet ved inflammatorisk sykdom hovedsakelig skyldes smerte, stivhet og redusert fysisk aktivitetsnivå eller om endringene kan tilskrives den inflammatoriske prosessen. Du får denne henvendelsen fordi du er pasient ved revmatologisk avdeling ved Diakonhjemmet Sykehus.
Diakonhjemmet Sykehus og Norges Idrettshøgskole er ansvarlige for studien.

Hva innebærer studien?
Du skal møte på Norges Idrettshøgskole to ganger, og undersøkelsene vil vare i ca. 1 time. Tidspunkter avtales individuelt. De to siste dagene før forsøket må du avstå fra all krevende fysisk aktivitet (trening). I tillegg vil du måtte møte på et privat røntgeninstitutt for å ta MR bilde av lårmuskulaturen, også denne timen vil avtales individuelt.

<u>Undersøkelsen</u>
Du vil gjennomgå følgende tester og undersøkelser:
Spørreskjema for å kartlegge relevant personlig bakgrunnsinformasjon og sykdomstilstand.
Bevegelighetstest: det vil bli gjennomført en sykdomsspesifikk bevegelighetstest som innebærer målinger av bevegelighet i rygg, nakke og hofter.

DXA: det vil bli gjennomført en DXA-analyse for å måle kroppssammensetningen. Denne testen innebærer at du ligger stille fullt påkledd i ca. 10 min.
Muskelfunksjonstest: testingen av muskelfunksjonen gjøres i et kneestrekkapparat som er låst ved 90◦ i kneleddet.
Muskelbiopsi: det vil bli tatt en muskelbiopsi av lårmuskulaturen som vil gjennomføres på følgende måte:

- Huden og bindevevet lokalbedøves der vevprøven skal taes.
- Et snitt på ca. 1-2 cm gjøres gjennom hud og muskelfascien.
- En nål med diameter på 6 mm føres inn (2-3 cm) og 1-3 små biter av muskulaturen tas ut (totalt 200 mg)
- Snittet lukkes med tape (strips).

Blodprøve

Eventuelle ulemper ved å delta
Deltakelse i prosjektet vil kreve en del tid og oppmerksomhet. Du må møte ved Norges Idrettshøgskole to ganger, og i tillegg vil du møte ved et privat røntgeninstitutt ved en anledning.
Vevsprøvetakninger (muskelbiopsier) medfører en liten infeksjonsfare, og ubehag/smerter kan oppleves under inngrepet. Du kan også oppleve lette til moderate smerter 1-2 døgn etter inngrepet. Du vil få et lite arr etter snittet i huden; arret vil sakte bli mindre tydelig. Enkelte personer vil kunne få en fortykning av huden i arrområdet.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Denne kodelisten vil fysisk være innelåst, slik at det kun er forskerne tilknyttet studien som har tilgang til den. Alle som får innsyn i informasjonen om deg har taushetsplikt. Innsamlede data vil bli anonymisert etter 5 år (kodelisten destrueres).
Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Biobank
Muskelbiopsiene vil bli oppbevart i en forskningsbiobank uten kommersielle interesser (vurdert av Regional Etisk komite). Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Prøvene vil bli lagret til 2019. Ansvarlig for biobanken er professor Truls Raastad ved seksjon for fysisk prestasjonsevne ved Norges Idrettshøgskole. Det biologiske materialet kan bare brukes etter godkjenning fra Regional komité for medisinsk og helsefaglig forskningsetikk (REK). Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger utleveres til Diakonhjemmet Sykehus.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte Kristine Røren Nordén tlf: 920 43 801.

Innsynsrett og oppbevaring av materialet
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver, opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Informasjon om utfallet av studien
Etter at data er samlet inn og analysert vil alle forsøkspersonene få tilsendt et informasjonsbrev der vi presenterer resultatene fra studien.

Forsikring
Deltakerne i prosjektet er forsikret dersom det skulle oppstå skade eller komplikasjoner som følge av deltakelse i forskningsprosjektet. Norges Idrettshøgskole er en statlig institusjon og er således selvassurandør. Dette innebærer at det er Norges Idrettshøgskole som dekker en eventuell erstatning og ikke et forsikringsselskap.

Finansiering
Analysene av muskelbiopsiene vil bli finansiert av Revmatologisk avdeling ved Diakonhjemmet Sykehus.

Publisering
Resultatene fra studien vil offentliggjøres i internasjonale, fagfellevurderte tidsskrift. Du vil få tilsendt artiklene dersom du ønsker det.

Samtykke
Hvis du har lest informasjonsskrivet og ønsker å være med som forsøksperson i prosjektet, ber vi deg om å undertegne «samtykke om deltakelse» og returnere dette til en av personene som er nevnt nedenfor. Du bekrefter samtidig at du har fått kopi av og lest denne informasjonen.

Det er frivillig å delta og du kan når som helst trekke deg fra prosjektet uten videre begrunnelse. Alle data vil, som nevnt ovenfor, bli avidentifisert før de blir lagt inn i en database og senere anonymisert.

Dersom du ønsker flere opplysninger kan du ta kontakt med Kristine Røren Nordén på tlf. 920 43 801 eller Silje Halvorsen Sveaas på tlf. 996 48 102.

Med vennlig hilsen

Kristine Røren Nordén (Mastergradsstudent i idrettsfysioterapi)
Silje Halvorsen Sveaas (Stipendiat)
Hanne Dagfinrud (Seniorforsker)
Truls Raastad (Professor)

Samtykkeerklæring følger på neste side.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Att. 3: *Informed consent form (controls)*

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Eventuelle ulemper ved å delta
Deltakelse i prosjektet vil kreve en del tid og oppmerksomhet. Du må møte ved Norges Idrettshøgskole to ganger, og i tillegg vil du møte ved et privat røntgeninstitutt ved en anledning.
Vevsprøvetakninger (muskelbiopsier) medfører en liten infeksjonsfare, og ubehag/smerter kan oppleves under inngrepet. Du kan også oppleve lette til moderate smerter 1-2 døgn etter inngrepet. Du vil få et lite arr etter snittet i huden; arret vil sakte bli mindre tydelig. Enkelte personer vil kunne få en fortykning av huden i arrområdet.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Denne kodelisten vil fysisk være innelåst, slik at det kun er forskerne tilknyttet studien som har tilgang til den. Alle som får innsyn i informasjonen om deg har taushetsplikt. Innsamlede data vil bli anonymisert etter 5 år (kodelisten destrueres).
Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Biobank
Muskelbiopsiene vil bli oppbevart i en forskningsbiobank uten kommersielle interesser (vurdert av Regional Etisk komite). Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Prøvene vil bli lagret til 2019. Ansvarlig for biobanken er professor Truls Raastad ved seksjon for fysisk prestasjonsevne ved Norges Idrettshøgskole. Det biologiske materialet kan bare brukes etter godkjenning fra Regional komité for medisinsk og helsefaglig forskningsetikk (REK). Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger utleveres til Diakonhjemmet Sykehus.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte Kristine Røren Nordén tlf: 920 43 801.

Innsynsrett og oppbevaring av materialet

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver, opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Informasjon om utfallet av studien
Etter at data er samlet inn og analysert vil alle forsøkspersonene få tilsendt et informasjonsbrev der vi presenterer resultatene fra studien.

Forsikring
Deltakerne i prosjektet er forsikret dersom det skulle oppstå skade eller komplikasjoner som følge av deltakelse i forskningsprosjektet. Norges Idrettshøgskole er en statlig institusjon og er således selvassurandør. Dette innebærer at det er Norges Idrettshøgskole som dekker en eventuell erstatning og ikke et forsikringsselskap.

Finansiering
Analysene av muskelbiopsiene vil bli finansiert av Revmatologisk avdeling ved Diakonhjemmet Sykehus.

Publisering
Resultatene fra studien vil offentliggjøres i internasjonale, fagfellevurderte tidsskrift. Du vil få tilsendt artiklene dersom du ønsker det.

Samtykke
Hvis du har lest informasjonsskrivet og ønsker å være med som forsøksperson i prosjektet, ber vi deg om å undertegne «samtykke om deltakelse» og returnere dette til en av personene som er nevnt nedenfor. Du bekrefter samtidig at du har fått kopi av og lest denne informasjonen.

Det er frivillig å delta og du kan når som helst trekke deg fra prosjektet uten videre begrunnelse. Alle data vil, som nevnt ovenfor, bli avidentifisert før de blir lagt inn i en database og senere anonymisert.

Dersom du ønsker flere opplysninger kan du ta kontakt med Kristine Røren Nordén på tlf. 920 43 801 eller Silje Halvorsen Sveaas på tlf. 996 48 102.

Med vennlig hilsen

Kristine Røren Nordén (Mastergradsstudent i idrettsfysioterapi)
Silje Halvorsen Sveaas (Stipendiat)
Hanne Dagfinrud (Seniorforsker)
Truls Raastad (Professor)

Samtykkeerklæring følger på neste side.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Att. 4: *Questionnaire including BASDAI and BASFI (patients)*

Muskelvev og muskelfunksjon ved spondyloartritt: Spørreskjema

Konsekvenser av spondyloartritt på muskelvev og muskelfunksjon

Vi ønsker å få din vurdering av egen helsetilstand. De første sidene inneholder spørsmål om personopplysninger, sykdomsaktivitet og fysisk funksjon.

Alle svarene er viktige. Dette er en undersøkelse hvor vi ønsker å få vite hva **DU** mener om **DIN EGEN** helsesituasjon

På forhånd takk for hjelpen!

Fyll ut dagens dato |__|__| |__|__| |__|__|__|__|
dag måned årstall

|__|__|__|__|__|
id. nr.

|__|__|__|
Initialer

Høyde:

Vekt:

BMI:

Personopplysninger

Deltakernr ☐☐☐☐☐☐ **Dato** ☐☐-☐☐-☐☐☐☐

GENERELLE SPØRSMÅL

1a. Hva er din nåværende sivilstand?

- ☐ Ugift / ikke samboende
- ☐ Ugift / samboende
- ☐ Gift
- ☐ Skilt
- ☐ Enkemann / enke

1b. Hvilken er din høyeste utdanning?

- ☐ Grunnskole
- ☐ Allmenn videregående skole
- ☐ Yrkesrettet videregående skole
- ☐ Høyskole eller universitet, mindre enn 4 år
- ☐ Høyskole eller universitet, mer enn 4 år

2. Røyker du?

- ☐ Nei, aldri røykt
- ☐ Nei, har røykt tidligere; (mnd.-år)
  - Startet ☐☐-☐☐☐☐
  - Sluttet ☐☐-☐☐☐☐
- ☐ Ja, startet ☐☐-☐☐☐☐

Røyker i gjennomsnitt ☐☐☐ sigaretter per dag

3. Hvilke medikamenter bruker du nå?

4. Har du noen sykdommer i tillegg til spondyloartritt?

ARBEIDE

4. Har du inntektsgivende arbeid nå? ☐ Ja ☐ Nei

Hvis nei, er du

- ☐ Elev/student
- ☐ Hjemmearbeidende
- ☐ Arbeidsledig
- ☐ Alderspensjonist
- ☐ Uføretrygdet

Vurdering av egen tilstand

Spørsmålene nedenfor gjelder hvordan du følte deg den siste uken. Marker ditt svar med å krysse i en rute ☒.

1. Hvordan vil du beskrive den generelle graden av utmattelse/tretthet du har erfart?

	0	1	2	3	4	5	6	7	8	9	10	
Ingen	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Svært høy

2. Hvordan vil du beskrive den generelle graden av smerter i nakke-, rygg eller hofter i forbindelse med ryggplager?

	0	1	2	3	4	5	6	7	8	9	10	
Ingen	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Svært høy

3. Hvordan vil du beskrive det generelle nivået av smerter/hevelse du har hatt i andre ledd enn nakken- ryggen eller hoftene?

	0	1	2	3	4	5	6	7	8	9	10	
Ingen	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Svært høy

4. Hvordan vil du beskrive den generelle graden av ubehag du har hatt på eventuelle steder som gjør vondt ved berøring eller trykk?

	0	1	2	3	4	5	6	7	8	9	10	
Ingen	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Svært høy

5. Hvordan vil du beskrive den generelle graden av stivhet du har opplevd om morgenen fra det tidspunktet du våkner?

	0	1	2	3	4	5	6	7	8	9	10	
Ingen	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Svært høy

6. Hvor lenge varer morgenstivheten fra det tidspunktet du våkner?

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0 timer					1 time					2 timer eller mer

7. Hvor aktiv var din sykdom i gjennomsnitt den siste uken?

	0	1	2	3	4	5	6	7	8	9	10	
Ikke aktiv	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Meget aktiv

Vurdering av egen funksjon

Spørsmålene nedenfor gjelder hvordan du følte deg den siste uken. Marker ditt svar med å krysse i en rute ☒.

1. Ta på strømper eller strømpebukser uten assistanse eller ved bruk av hjelpemidler (for eksempel strømpepåtrekker)

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

2. Bøye deg fremover fra midjen for å plukke opp en penn fra gulvet uten å bruke et hjelpemiddel

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

3. Nå opp til en høythengende hylle uten bruk av hjelpemidler (f.eks. gripetang)

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

4. Reise deg fra en spisebordsstol uten armlener eller annen hjelp?

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

5. Reise deg opp fra liggende stilling på gulvet uten hjelp

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

6. Stå oppreist uten støtte i 10 min. uten å få ubehag

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

7. Gå opp 12-15 trappetrinn uten å bruke rekkverk eller gåstøtte. En fot på hvert trinn

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

8. Se deg over skulderen uten å vri kroppen

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

9. Utføre fysisk krevende aktiviteter (f.eks. fysioterapiøvelser, hagearbeid eller sport)

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

10. Utføre en hel dags aktiviteter enten hjemme eller på arbeid

	0	1	2	3	4	5	6	7	8	9	10	
Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Umulig

Treningsvaner

1a.	I løpet av en vanlig uke; hvor ofte trener du kondisjon med en intensitet som gjør at du blir merkbart andpusten?	☐ ☐ ☐ ☐	Aldri eller meget sjelden 1-2 ganger per uke 3-5 ganger per uke Mer enn 5 ganger pr. uke
1b.	I løpet av en vanlig uke; hvor ofte trener du styrke med vekter, strikk, slynger eller egen kroppsvekt som motstand?	☐ ☐ ☐ ☐	Aldri eller meget sjelden 1-2 ganger per uke 3-5 ganger per uke Mer enn 5 ganger pr. uke

Att. 5: *Questionnaire (controls)*

Muskelvev og muskelfunksjon ved spondyloartritt: Spørreskjema

Konsekvenser av spondyloartritt på muskelvev og muskelfunksjon

Vi ønsker å få din vurdering av egen helsetilstand. De første sidene inneholder spørsmål om personopplysninger, sykdomsaktivitet og fysisk funksjon.

Alle svarene er viktige. Dette er en undersøkelse hvor vi ønsker å få vite hva **DU** mener om **DIN EGEN** helsesituasjon

På forhånd takk for hjelpen!

Fyll ut dagens dato |__|__| |__|__| |__|__|__|__|
dag måned årstall

|__|__|__|__|__|__|
id. nr.

|__|__|__|
Initialer

Høyde:

Vekt:

BMI:

Personopplysninger

Deltakernr ☐☐☐☐☐☐ **Dato** ☐☐-☐☐-☐☐☐☐

GENERELLE SPØRSMÅL

1a. Hva er din nåværende sivilstand?

- ☐ Ugift / ikke samboende
- ☐ Ugift / samboende
- ☐ Gift
- ☐ Skilt
- ☐ Enkemann / enke

1b. Hvilken er din høyeste utdanning?

- ☐ Grunnskole
- ☐ Allmenn videregående skole
- ☐ Yrkesrettet videregående skole
- ☐ Høyskole eller universitet, mindre enn 4 år
- ☐ Høyskole eller universitet, mer enn 4 år

2. Røyker du?

- ☐ Nei, aldri røykt
- ☐ Nei, har røykt tidligere; (mnd.-år)
  - Startet ☐☐-☐☐☐☐
  - Sluttet ☐☐-☐☐☐☐
- ☐ Ja, startet ☐☐-☐☐☐☐

Røyker i gjennomsnitt ☐☐☐ sigaretter per dag

3. Hvilke medikamenter bruker du nå?

ARBEIDE

4. Har du inntektsgivende arbeid nå? ☐ Ja ☐ Nei

Hvis nei, er du

- ☐ Elev/student
- ☐ Hjemmearbeidende
- ☐ Arbeidsledig
- ☐ Alderspensjonist
- ☐ Uføretrygdet

Treningsvaner

1a. I løpet av en vanlig uke; hvor ofte trener du kondisjon med en intensitet som gjør at du blir merkbart andpusten?

- ☐ Aldri eller meget sjelden
- ☐ 1-2 ganger per uke
- ☐ 3-5 ganger per uke
- ☐ Mer enn 5 ganger pr. uke

1b. I løpet av en vanlig uke; ☐ Aldri eller meget sjelden

hvor ofte trener du styrke med vekter, strikk, slynger eller egen kroppsvekt som motstand?	☐	1-2 ganger per uke
	☐	3-5 ganger per uke
	☐	Mer enn 5 ganger pr. uke

Att. 6: *Bath Ankylosing Spondylitis Metrology Index (BASMI)*

BASMI

Bath Ankylosing Spondylitis Metrology Index, a combined index to assess the spinal mobility in patients with ankylosing spondylitis *)

ASIF
Ankylosing Spondylitis International Federation

Name: _____

Date: _____

1. **Lateral lumbar flexion**: Patient stands with heels and buttocks touching the wall, knees straight, shoulders back, hands by the side. The patient is then asked to bend to the right side as far as possible without lifting the left foot/heel or flexing the right knee, and maintaining a straight posture with heels, buttocks, and shoulders against the wall. The distance from the third fingertip to the floor when patient bends to the side, is subtracted from the distance when patient stands upright. The manoeuvre is repeated on the left side.

Assessment:	> 20	18–20	15,9–18,9	13,8–15,8	11,7–13,79	9,6–11,6	7,5–9,5	5,4–7,4	3,3–5,3	1,2–3,2	< 1,2
Score:	0	1	2	3	4	5	6	7	8	9	10

mean of right/left: ____

2. **Tragus-to-wall distance**: Maintain same starting position as above. Ensure head in as neutral position (anatomical alignment) as possible, chin drawn in as far as possible. Measure distance between tragus of the ear and wall on both sides, using a rigid ruler. Ensure no cervical extension, rotation, flexion or side flexion occurs.

Assessment:	< 10	10–12	13–15	16–18	19–21	22–24	25–27	28–30	31–33	34–36	> 36
Score:	0	1	2	3	4	5	6	7	8	9	10

mean of right/left: ____

3. **Lumbar flexion (modified Schober)**: With the patient standing upright, place a mark at the lumbosacral junction (at the level of the dimples of Venus on both sides). Further marks are placed 5 cm below and 10 cm above [1]. Measure the distraction of these two marks when the patient bends forward as far as possible, keeping the knees traight.

[1]) Among the "modified Schober"s published in the literature, the modification recommended by Macrae and Wright is used.

Assessment:	> 7,0	6,4–7,0	5,7–6,3	5,0–5,6	4,3–4,9	3,6–4,2	2,9–3,5	2,2–2,8	1,5–2,1	0,8–1,4	< 0,8
Score:	0	1	2	3	4	5	6	7	8	9	10

____

4. **Maximal intermalleolar distance:** Patient supine on the floor or a wide plinth, with the knees straight and the feet pointing straight up. Patient is asked to separate legs along the resting surface as far as possible. Distance between medial malleoli is measured.

Assessment:	> 119	110–119	100–109	90–99	80–89	70–79	60–69	50–59	40–49	30–39	< 30
Score:	0	1	2	3	4	5	6	7	8	9	10

____

5. **Cervical rotation:** Patient supine on plinth, head in neutral position, forehead horizontal (if necessary head on pillow or foam block to allow this, must be documented for future reassessments). Gravity goniometer placed centrally on the forehead. Patient rotates head as far as possible, keeping shoulders still, ensure no neck flexion or side flexion occurs.

> 85,0	76,6–85	68,1–76,5	59,6–68,0	51,1–59,5	42,6–51,0	34,1–42,5	25,6–34,0	17,1–25,5	8,6–17,0	< 8,6
0	1	2	3	4	5	6	7	8	9	10

mean of right/left: ____

BASMI: (mean of 5 scores) ____

*) Remark:
In the literature (Jenkinson et al: J Rheumatol 1994;21:1694–1698 and Jones et al: J Rheumatol 1995;22:1609) two different BASMI definitions have been published where the same measurement results lead to different BASMI values. The above is based on the newer definition of1995 with scores 0 to 10 for each component.

Ankylosing Spondylitis International Federation
World-wide network of societies of patients suffering from ankylosing spondylitis or related diseases
www.spondylitis-international.org

Att. 7: *Information on muscle biopsy wound care*

Informasjon til forsøkspersoner

- Stell av sår etter muskelbiopsi

Du er nå forsøksperson i prosjektet *«Har pasienter med spondyloartritt endringer i muskelvev og muskelfunksjon som følge av sin inflammatoriske revmatiske sykdom?»* der vi har tatt muskelprøver (biopsi) fra knestrekkerne (m. vastus lateralis). Dette er et lite inngrep som normalt ikke har noen negative følger, bortsett fra sår muskulatur noen dager. Imidlertid er det alltid en risiko for infeksjon ved slike inngrep. Vi ber deg derfor å følge rådene under. Om det skulle oppstå noe av medisinsk karakter som du tror kan settes i sammenheng med forsøket må du kontakte Truls.

Det er nå viktig at du tar de forhåndsregler som skal til for at sårene dine skal gro godt. Følgende punkter er viktige:

1. Hold såret tørt. Du bør ikke vaske området ved sårene eller dusje slik at tapen rundt sårene blir våte. Vann i dette området vil øke faren for infeksjon og det vil også føre til at tapen som skal holde sårflatene sammen løsner. Du kan dusje, men sørg for at du ikke får vann i nærheten av sårene (dusj forsiktig, bruk evt gladpack el ☺).
2. Unngå trykk eller store drag i huden rundt såret.
3. Om lag én uke etter at såret ble laget skal det ha dannet seg en skorpe som er så sterk at hudflatene holdes sammen og vann ikke trenger inn i såret. Først da kan du dusje på vanlig måte. Tilheling på 1 uke forutsetter selvfølgelig at punkt 1 er fulgt.

Hvis ”stripsene” som holder såret sammen løsner før det har gått en uke bør du få på nye ”stripps”. Ta da kontakt med én av kontaktpersonene under.

Truls Raastad: 91368896