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Cardiometabolic risk profile and body composition in early rheumatoid arthritis

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2. ABBREVIATIONS

24 HDR	24-hour dietary recall
ACPA	anti cyclic protein antibodies
ACR	American College of Rheumatology
ALM	appendicular lean mass
ALMI	appendicular lean mass index
BC	body composition
BFP	body fat percentage
BMI	body mass index
CI	confidence interval
COBRA	Combination therapy in early rheumatoid arthritis
CORRONA	The Consortium of Rheumatology Researchers of North America
CRP	C-reactive protein
CV	cardiovascular
CVD	cardiovascular disease
DAS 28	disease activity score based on 28 joints
DEXA	dual- energy x-ray absorptiometry
DMARD	disease- modifying anti- rheumatic drug
DNA	deoxyribonucleic acid
ERA	early rheumatoid arthritis
ESR	erythrocyte sedimentation rate
EULAR	European League against Rheumatism
EWGSOP	European Working Group on Sarcopenia in Older People
FFM	fat free mass
FFMI	fat free mass index
FMI	fat mass index
GCS	glucocorticosteroid
HAQ-DI	health assessment questionnaire disability index
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
IL	interleukin
IPAQ	international physical activity questionnaire
LDL	low-density lipoprotein
MRI	magnetic resonance imaging
MetS	metabolic syndrome
NCEP-ATP III	National Cholesterol Education Program Adult Treatment Panel-III
NHANES	National Health and Nutrition Examination Survey
NSAID	non- steroidal anti- inflammatory drug

OR	odds ratio
RA	rheumatoid arthritis
RF	rheumatoid factor
RR	risk ratio
TG	triglycerides
TNF	tumor necrosis factor
WHO	World Health Organization

3. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease with a prevalence of 0.5–2%. The disease is characterized by an autoimmune process starting in the preclinical stage and resulting in damage to synovium- containing joints. Despite its predominant articular involvement, RA is a systemic disease with a wide variety of extra-articular features and comorbidities.

The treatment of RA has dramatically evolved over the past decades (Smolen et al., 2017). RA treatment is currently targeted to remission induction through a threat to target strategy – an aim that was unreachable before (Smolen et al., 2016). Though advances in the treatment of joint disease have improved the quality of life of patients with RA, non-articular features still contribute to the physical disability, psychological morbidity and premature mortality of RA (Cutolo et al., 2014; Giles, 2019).

Although joint inflammation and destruction are responsible for disability and loss of quality of life, the main cause of excess mortality in RA is cardiovascular disease (CVD), accounting for nearly half of all the deaths, and being an important contributor to a mortality gap between patients with RA and the general population not entirely explained by traditional cardiovascular risk factors such as obesity or inflammatory activity (Agca et al., 2017; Cutolo et al., 2014; Giles, 2019; Sokka, T. et al., 2008; Summers et al., 2010).

The importance of cardiometabolic risk factors and alterations in body composition in the initial stage of RA is seldom the focus of research, so our study was undertaken to determine the important connections between these factors and changes.

4. LITERATURE REVIEW

4.1. Early rheumatoid arthritis

The first stage of the development of RA is the acquisition of genetic risk factors for the disease at conception, followed by gene-environmental interactions later in life. Smoking, respiratory mucosal inflammation, periodontitis and an altered gut microbiome are among the environmental factors potentially triggering autoimmune response (Tracy et al., 2017).

A prolonged state of autoimmunity precedes the clinical onset of RA. The development of seropositivity-production of autoantibodies targeted against citrullinated proteins (ACPA) and Fc portion of IgG (rheumatoid factor- RF) and T-cell infiltration with an increased expression of pro-inflammatory cytokines and chemokines has been demonstrated in this preclinical stage, years before symptoms of synovitis (Bijlsma et al., 2015; Tracy et al., 2017). Ultrasound and magnetic resonance imaging can visualize synovitis in clinically normal joints of patients later developing RA (Bijlsma et al., 2015).

The concept of a "window of opportunity" refers to a period of weeks to months early in the course of the disease when the disease process can be altered or possibly even reversed. Currently, a symptom duration of up to 12–24 months is considered early, but the real duration of "the window of opportunity" is unclear, as significant damage can appear even in the first weeks to months after the onset of symptoms. The prognosis of early arthritis is often difficult to predict (Bijlsma et al., 2015), and a combination of clinical, laboratory and radiographic parameters have to be taken account to predict the outcome, although classification criteria for RA aid in diagnosing the disease earlier (Aletaha et al., 2010).

Regularly updated and widely accepted treatment recommendations have been developed in consensus between European League against Rheumatism (EULAR) and the American College of Rheumatology (ACR) to reach optimal treatment outcomes, aiming to start disease modifying treatment before the onset of erosion in order to reduce, or even prevent, the risk of further joint damage and disability (Bijlsma et al., 2015; Combe et al., 2017) (Smolen et al., 2016, 2017).

According to current recommendations on the management of early arthritis, disease-modifying anti-rheumatic drugs (DMARDs) should be ideally started within 3 months of the onset of the first symptoms (Combe et al., 2017). Prescribing DMARDs for early chronic inflammatory arthritis, preferably before the onset of erosion, can reduce or even prevent the risk of (further) joint damage and disability (Bijlsma et al., 2015; Combe et al., 2017).

4.2. Non-articular features of rheumatoid arthritis

The incidence and severity of several non-articular manifestations, such as rheumatoid vasculitis and amyloidosis, has declined, but this does not seem to be shared by all RA comorbidities, such as accelerated atherosclerosis, interstitial lung disease, and sarcopenia that can already present in the pre-clinical or earliest stage of RA (Giles, 2019). Commonly used therapies, such as glucocorticoids (GCS) and non-steroidal anti-inflammatory drugs (NSAIDs), may themselves contribute to the development of dyslipidemia, hyperglycemia, atherosclerosis and osteoporosis.

There is a lack of consensus how to define and classify the non-articular features of RA, and how to distinguish extra-articular manifestations form comorbidities (Giles, 2019; Prete et al., 2011). Classical extra-articular manifestations (vasculitis, Sjogren's syndrome, interstitial lung disease, and nodules) are directly driven by the cellular infiltration of activated immune effector cells into affected tissues, leading to structural damage and organ dysfunction (Giles, 2019). Comorbidities appear due to the effect of chronic inflammation – constitutional symptoms such as fatigue, infections, anemia, depression and other psychosocial manifestations are the ones seen most often. However, whether accelerated atherosclerosis, osteoporosis, and muscle loss are RA-associated comorbidities or extra-articular manifestations is still under discussion (Giles, 2019).

4.3. Cardiovascular morbidity and mortality in rheumatoid arthritis

A large prospective population-based cohort study of CVD end-points performed in England (12,120 individuals with RA and 121,191 comparators) found that RA patients had higher adjusted incidence rates of myocardial infarction (1.43), unheralded coronary death (1.60), heart failure (1.61) and cardiac arrest (2.26) (Pujades-Rodriguez et al., 2016). In addition, RA patients have more subclinical atherosclerosis and silent myocardial disease compared to the general population, which may not be accounted for during CVD risk evaluation (Błyszczuk & Szekanecz, 2020; Crowson et al., 2018). It has been suggested that the added risk for cardiovascular disease may precede the onset of synovitis (Maradit-Kremers et al., 2005).

There seems to be an important geographical heterogeneity in CVD risk in RA due to variations in both non-modifiable and modifiable characteristics of patient populations (Pappas et al., 2018). Looking into CORRONA registry data, the prevalence of traditional individual CVD risk factors (hypertension, smoking, hyperlipidemia, and hyperglycemia) and high disease activity was found to be higher in RA patients living in Eastern Europe and the finding was associated with CV risk more than twice that of subjects enrolled in USA, more than three times higher than in participants from Latin America, and more than seven times higher than in Indian participants (Pappas et al., 2018).

RA has been found to increase cardiovascular (CV) risk independently of traditional risk factors (age, male gender, smoking, history of CV disease, family history, diabetes, and hypercholesterolemia), with a RR of about 1.5 suggesting that different pathogenic mechanisms are responsible for the progression of cardiovascular disease among patients with RA. (Agca et al., 2017; Avina-Zubieta et al., 2012; Błyszczuk & Szekanecz, 2020; Hippisley-Cox et al., 2008; Piepoli et al., 2016; Yoshida et al., 2019). There seems to be a complex and often bidirectional interaction between traditional and RA related risk factors, contributing to an increased CV risk (del Rincón et al., 2015; England, Thiele, et al., 2018). In 2017, Crowson estimated that traditional CVD risk factors explain 49% of the risk and disease specific characteristics add 30% with a combined value of 70% in CVD risk prediction in established RA (Crowson et al., 2018).

RA patients have an increased rate of traditional risk factors, but their relative contribution to CVD risk seems less in patients with RA than in the general population (Błyszczuk & Szekanecz, 2020; Boyer et al., 2011; Solomon et al., 2003; Yu et al., 2018). Systemic inflammation through direct effect on the vessel wall and via modulation of traditional risk factors seems to have a pivotal role in the excess risk (Błyszczuk & Szekanecz, 2020; Nurmohamed et al., 2015; Piepoli et al., 2016; Skeoch & Bruce, 2015).

CVD risk has been reported to increase even in the first year following RA onset (England, Thiele, et al., 2018; Mantel et al., 2015). Circulating inflammatory mediators may affect arterial walls, promoting the development of atherosclerosis due to enhanced endothelial dysfunction, plaque formation, destabilization and rupture. Atherosclerosis develops as a diffuse, systemic process and is already present many years before the first clinical manifestations occur, being more prevalent in RA than in general population (Skeoch & Bruce, 2015; van Sijl et al., 2011). There is evidence of the accelerated atherogenic process already taking place in the preclinical stage of RA but a lack of data from large-scale prospective studies (Bartoloni et al., 2010; Hannawi et al., 2007; Kerola et al., 2012).

Additionally, some of the medications used in the treatment of RA – particularly non-steroidal anti-inflammatory drugs and corticosteroids, are associated with higher CV morbidity (Agca et al., 2017; Błyszczuk & Szekanecz, 2020). Genetic predisposition could also be important – it has been hypothesized that the two conditions share genetic susceptibility factors but investigations in this area are still in their early stages (Skeoch & Bruce, 2015). CVD risk factors and RA characteristics explain about 70% of the risk for CVD outcomes, leaving 30% unaccounted for (Crowson et al., 2018).

Widely used validated CV risk calculators for the general population tend to underestimate the added risk and are of limited value in RA. There are currently no disease-specific prediction models with proven accuracy available. Even RA-specific CV risk scores have failed to be superior to general risk evaluation tools (Agca et al., 2017; Crowson et al., 2017; Hippisley-Cox et al., 2008; Piepoli et al., 2016). Risk estimations from CV risk algorithms have found to deviate from observed risk, even in patients with early RA (Arts et al., 2015). The latest EULAR guidelines for CV risk management suggest using a multiplication factor of 1.5

for all patients with RA when using CV risk calculators created for the general population (Agca et al., 2017). It is possible that this approach might overestimate CV risk in some RA patients, but might underestimate it in other RA subgroups (seropositive, highly active disease) (Hollan et al., 2019).

RA is traditionally believed to confer a 40–50% higher risk of mortality, a risk increase present even in the disease's early stage (Abhishek et al., 2018; England, Thiele, et al., 2018; Kerola et al., 2012). A recent study evaluated the mortality rate in 5 years after an RA diagnosis from 1990 to 2009 compared to the general population and found that subjects diagnosed in 2007–2009 had a 15% excess mortality risk that is significantly lower than the 32–46% mortality risk found in cases incidental to earlier years (Abhishek et al., 2018).

There is a trend towards decreasing CV mortality in incidental cases of RA. The RA death rate has declined in patients diagnosed and treated early with tight control of the inflammatory process according to current standards (Abhishek et al., 2018; Holmqvist et al., 2018; Kerola et al., 2015; Lacaille et al., 2017; Meek et al., 2014; Myasoedova et al., 2017). In a study by Myasoedova et al., a 58% decline in CV mortality and 83% decline in coronary heart related mortality in patients with RA onset in 2000–07 vs. 1990–99 was reported in men and women (adjusted for CV risk factors, age and seropositivity) (Myasoedova et al., 2017). At the same time, the mortality outcome of patients with established RA has remained unchanged (van den Hoek et al., 2016) and the gap in mortality in RA compared with the general population is still apparent (Holmqvist et al., 2018).

There is a possibility that the effect on mortality appears due to the improved recognition and management of CV risk in RA patients – especially those with the highest degree of risk (Agca et al., 2017). The awareness of excess CVD risk in inflammatory disease has grown in recent years and peaked with EULAR recommendations for cardiovascular disease risk management in patients with RA (Agca et al., 2017; Peters et al., 2010). It is still too early to generalize stating that CV mortality in RA is declining, as data from large population-based cohorts of patients with RA with long-term follow-up is missing, and there is no information available on the time trends of subclinical atherosclerosis.

4.4. Differences in cardiometabolic risk profile between general population and patients with rheumatoid arthritis

4.4.1. Hypertension

Hypertension affects about 1 billion people worldwide, and has one of the strongest associations with cardiovascular disease in general population (Panoulas et al., 2008). There are several factors playing a role in the development of hypertension in RA. Chronic inflammatory status, genetic factors, low physical activity, smoking and the use of anti-inflammatory analgesics and glucocorticosteroids may synergistically lead to hypertension in patients with RA (Panoulas et al., 2008; Peters et al., 2010). The reported prevalence of hypertension in RA has been widely

variable in different studies, ranging from 4% to 73% (Boyer et al., 2011; Nurmohamed et al., 2015). Several studies have demonstrated that the elevated blood pressure associated with subclinical atherosclerosis is one of the most significant independent predictors of CVD in RA (relative risk for CVD from 1.49 to 4.3) (Boyer et al., 2011; Crowson et al., 2018; Panoulas et al., 2008). Interestingly, in a meta-analysis published in 2011, no difference was found in the prevalence of hypertension between RA patients and the general population (Boyer et al., 2011).

At the same time, it is known that hypertension among patients with RA might be underdiagnosed and suboptimally treated (Crowson et al., 2017; Ikdahl et al., 2019; Nurmohamed et al., 2015; Pappas et al., 2018). The reported prevalence of treated hypertension has found to be widely variable, with rates ranging from 21% to 80% of RA patients with elevated blood pressure using antihypertensive treatment in different studies (Panoulas et al., 2008; Pappas et al., 2018).

4.4.2. Dyslipidemia

Dyslipidemia leading to atherosclerotic plaque development, and characterized by high total and low-density lipoprotein (LDL) cholesterol, hypertriglyceridemia and low high-density lipoprotein (HDL), is an established predictor of CVD in the general population (Liao & Solomon, 2013).

The prevalence of hyperlipidemia does not seem to be higher in RA patients compared to the general population, but chronic active inflammation is associated with hypertriglyceridemia and low HDL levels. This unfavorable atherogenic profile has been found in the preclinical state of RA (Boyer et al., 2011; Liao & Solomon, 2013; Peters et al., 2010) and even 10 years before the onset of the disease in donors later diagnosed with RA, in one study (Halm et al., 2007). It is not known whether the change in lipids is associated with the development of RA through a common socioeconomic (lifestyle) or genetic background.

Active inflammation could impair the antioxidant action of HDL, decreasing its protective capacity further and leading to accelerated atherogenesis (Kerekes et al., 2014). Some conventional (hydroxychloroquine) and biological disease modifying drugs have been shown to correct impairments in the triglyceride/HDL ratio and thus have a potential for stabilizing the atherogenic profile (Bissell et al., 2016; Peters et al., 2010).

Complicating matters is the fact that the low levels of total and LDL cholesterol often seen in active RA (and reported even before the onset of RA) have been linked to an increased risk of CVD – a phenomenon called the lipid paradox, with a U-shaped relationship between cholesterol quantity and cardiovascular morbidity (Crowson et al., 2018; England, Thiele, et al., 2018; Hollan et al., 2019; Kerekes et al., 2014; Liao & Solomon, 2013; Myasoedova et al., 2010). Taking this into account, statin therapy may not decrease CV risk in RA in a level seen in the general population.

4.4.3. Adiposity

Obesity is a recognized risk factor for CVD in the general population. Optimal survival is achieved at a body mass index (BMI) of 22.5–25 kg/m^2 with reductions in life expectancy of 3 and 10 years in individuals with moderate and extreme obesity, respectively (Huxley et al., 2010; Prospective Studies Collaboration, 2009). The prevalence of obesity has increased two- to three-fold over the last 30 years (Timmis et al., 2019). In 2016, 39% of the world's adult population was overweight according to World Health Organization (WHO) data (WHO, 2020). Previous research has shown that in Estonia, 29% of men and 34% of women are classified as obese (Eglit et al., 2013).

Adipose tissue is the main energy storage unit of the body, and additionally serves to produce adipokines, a type of bioactive hormone (Laakso, 2015; Van de Voorde et al., 2013). Adipokines are the main mediators in interaction between adipose tissue, the heart and vasculature. Aberrant production of these mediators could be the key link between obesity and elevated CV risk – either directly leading to endothelial dysfunction and atherosclerosis, or through inducing insulin resistance, type 2 diabetes, hypercoagulation, hyperlipidemia and hypertension (Patel et al., 2016; Van de Voorde et al., 2013).

Individuals with similar BMI can have different CV risks due to differences in body fat distribution, as adipose tissue located in different areas can vary in adipokine production profiles (Van de Voorde et al., 2013). Measures of visceral adiposity have been suggested to be superior to BMI in predicting CV risk (Huxley et al., 2010; C. M. Y. Lee et al., 2008). Visceral fat is probably the type presenting with the most pro-atherogenic profile through adipose tissue inflammation, leading to a range of metabolic abnormalities, including decreased glucose tolerance, insulin resistance and dyslipidemia – risk factors for type 2 diabetes and CVD (Antonopoulos & Tousoulis, 2017; Huxley et al., 2010). At the same time, fat accumulation in the hips and thighs has little or no effect on CV risk. The different patterns of fat distribution explain the gender ("apple type"– fat distribution with excess visceral fat in men and "pear type" in women) specific differences in CV mortality and also hint at what lies behind geographical differences in CV risk profiles – for example, Asians have higher CV risk profiles with elevated visceral fat mass, even when not overweight (Van de Voorde et al., 2013).

The question of whether individuals with RA have a higher BMI and prevalence of overweight and obesity compared with the general population is controversial (Liao & Solomon, 2013). There is some evidence of modest associations between obesity and the development of RA (George & Baker, 2016) and lower response rates in obese patients treated with both biologic and non-biologic therapy, even after adjustments for age, sex, smoking, and seropositivity (George & Baker, 2016; Heimans et al., 2013; Sandberg et al., 2014). No clear evidence behind the mechanism of the association between obesity, incidence of RA, and poor response to therapy has been established (George & Baker, 2016).

Some studies have shown a higher prevalence of RA in obese subjects (Ljung & Rantapää-Dahlqvist, 2016; Pedersen et al., 2006; Symmons et al., 1997; Voigt

et al., 1994), while others have reported the opposite (Cerhan et al., 2002; George & Baker, 2016; Hernández Avila et al., 1990; Liao & Solomon, 2013; Rodríguez et al., 2009; Turesson et al., 2016). In a meta-analysis, a relative risk of 1.31 (95% CI 1.12–1.53) for RA was found for obese subjects (Qin et al., 2015).

In some studies, only an association between obesity and seronegative RA has been shown (Lahiri et al., 2014; Pedersen et al., 2006). Obesity has been associated with elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values related to fat mass and not RA disease activity (George et al., 2017), and also higher patient-reported outcomes, including increased pain, fatigue and lower quality of life scores (but not swollen joint counts) independent of disease activity (Katz, 2017; Levitsky et al., 2017; Liu et al., 2017). It can be hypothesized that it is likely that some patients in these studies have been misclassified and do not actually have inflammatory arthritis, as radiographic studies have demonstrated a lower risk of joint damage in obese patients despite a clinically poor response to therapy (Baker et al., 2011; George et al., 2017).

When looking into the data on the body composition of RA patients, it is evident that they have more body fat for a given BMI than healthy controls – frequently presenting as abdominal obesity with excess visceral fat (Giles et al., 2010; Kerekes et al., 2014; Liao & Solomon, 2013). While obese individuals with RA are commonly seronegative, with less erosive disease, abnormal body fat distribution is associated with higher disease activity and more severe RA (Giles et al., 2010; Liao & Solomon, 2013). Excess visceral fat could be an important contributor to CV risk elevation in patients with RA.

Obesity has been associated with decreased CVD mortality in patients with established RA (England et al., 2016; Escalante A et al., 2005; George & Baker, 2016; Wolfe & Michaud, 2012) but data on early arthritis are lacking (Kerekes et al., 2014).

4.4.4. Hyperglycemia

Hyperglycemia and type 2 diabetes have been reported to be precursors to CV disease. In diabetic patients, 65% of deaths are found to be associated with CVD (Patel et al., 2016). The global prevalence of diabetes has nearly doubled since 1980, growing to 8.5% in the adult population in 2016 (Roglic & World Health Organization, 2016). Using aggressive therapy for diabetes, the risk of CVD is reduced by only about 42% – possibly due to the occurrence of systemic insulin resistance, leading to micro and macrovascular complications (Patel et al., 2016).

In most of the studies looking into the presence of diabetes in RA, an association between the two conditions has been found (Nicolau et al., 2017). In a meta-analysis, the odds of diabetes in RA was 1.74 (95% CI 1.22, 2.50) times higher than in the general population (Boyer et al., 2011). Interestingly in a large study looking into data in a UK general population database, the hazard ratio for diabetes in RA was 1.12 (95% CI 1.01, 1.25), but after adjustment to BMI, smoking, alcohol, glucocorticoid usage, and co-morbidities, the added risk

disappeared (HR 0.94 (95% CI 0.84, 1.06)) (Dubreuil et al., 2014) suggesting lifestyle factors play a role in the development of diabetes (Nicolau et al., 2017).

4.4.5. Low physical activity

Lack of exercise is an emerging pandemic associated with 5.3 million deaths per year through many adverse health conditions (I.-M. Lee et al., 2012). In a large meta-analysis, physical activity was associated with a risk reduction for CVD of 35% in the general population (Nocon et al., 2008). Exercise has a beneficial effect on body weight and visceral adipose tissue (Verheggen et al., 2016), cholesterol levels (Mann et al., 2014), blood pressure (Cornelissen & Smart, 2013) and glucose metabolism (Boulé et al., 2001).

Patients with RA are less physically active compared with healthy controls (Hernández-Hernández et al., 2014; Sokka T. et al., 2008; Verhoeven et al., 2016) due to the pain and loss of function caused by active inflammation, joint damage or fear of potential harm. It has been found that a low level of physical activity before the onset of RA is associated with a higher disease burden, some studies even suggest that physical activity can protect against the development of RA (Verhoeven et al., 2016). Exercise has a potential benefit in reducing the burden of atherosclerosis in RA (Metsios et al., 2019; Verhoeven et al., 2016), and is promoted as an integral part of standard care for chronic inflammatory arthritis in the 2018 EULAR recommendations for physical activity (Osthoff et al., 2018).

4.4.6. Smoking

Smoking is one of the most important cardiovascular risk factors, and also one of the most established risk factors for the development of RA, due to gene-environment interaction via the induction of citrullination in the lungs of patients carrying the shared epitope of HLA-DRB1 (Hedström et al., 2018). Smoking increases the risk of not only ACPA positive (OR 1.9, 95% CI 1.7, 2.1), but also ACPA negative, RA (OR 1.3, 95% CI 1.2, 1.5). The risk of development of ACPA positive RA persists even 20 years after the cessation of smoking (Hedström et al., 2018).

Current and former smoking is associated with an increased risk for the development of cardiovascular disease in patients with RA, with a higher risk in men than women (Agca et al., 2017; Crowson et al., 2018; Kerola et al., 2012).

4.4.7. Metabolic syndrome

Metabolic syndrome (MetS), the clustering of metabolic disturbances like hypertension, hyperglycemia, and gout, was first described in the 1920 by the Swedish physician Eskil Kylin (R. H. Eckel et al., 2005). The concept of metabolic

syndrome was later established by Gerald Reaven in 1988, under the name of "Syndrome X," which referred to co-occurring impaired glucose metabolism, insulin resistance, central obesity, dyslipidemia, and hypertension, leading to a higher CV risk than the sum of its individual components (R. H. Eckel et al., 2005; Isomaa et al., 2001).

Metabolic syndrome in general population

Over the recent decades, a striking increase in the prevalence of MetS has appeared, largely due to the worldwide obesity epidemic. Currently around 25% of the world's population has been reported to have metabolic syndrome (Ferraz-Amaro et al., 2013; Saklayen, 2018). In Estonia, the prevalence of MetS has been reported to be 28% (95% C.I 24.0, 32.1), a bit higher in men (30%) and somewhat lower in women (25%) (Eglit et al., 2012).

MetS has been shown to be a strong predictor of diabetes, cardiovascular disease and increased risk of (age, smoking and cholesterol adjusted) mortality in several prospective studies and meta-analyses (R. H. Eckel et al., 2005; Galassi et al., 2006). The presence of MetS is associated with a twofold increase in cardiovascular outcomes (CVD, CVD mortality, stroke and myocardial infarction) and a 1.5-fold increase in all-cause mortality among the general population (Mottillo et al., 2010).

There are several definitions for metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III – NCEP-ATP III 2001, 2004; World Health Organization, International Diabetes Federation, and European group for the Study of Insulin Resistance), but they have proven to be of similar accuracy in cardiovascular risk assessment (Ferraz-Amaro et al., 2013). According to the easiest to implement and most widely used criteria, the NCEP-ATP III, metabolic syndrome is defined by the presence of hyperglycemia (fasting plasma glucose levels ≥5.6 mmol/l), central obesity (waist circumference ≥90 cm in men, and ≥80 cm in women), low HDL levels (<1.03 mmol/l in men, <1.29 mmol/l in women), high total triglyceride (TG) levels (≥1.7 mmol/l), and elevated blood pressure (≥130/85 mmHg) or taking antihypertensive drugs ("Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report," 2002).

The only study found evaluating the performance of different criteria for MetS in cardiovascular risk prediction in RA, reported that the WHO criteria were superior to the NCEP-ATP III definition in predicting increased intima-media thickness (Dessein et al., 2006). The WHO criteria differ from the NCEP-ATP III criteria by mandating the presence of insulin resistance, taking into account total obesity instead of central obesity and adding the presence of microalbuminuria to the model (Alberti & Zimmet, 1998). As insulin resistance is a prerequisite for diagnosing MetS according to the WHO criteria, it is unclear if the added risk can be attributed to insulin resistance and how much MetS adds as a complete syndrome.

Metabolic syndrome in RA

There have been several studies investigating the presence of MetS in RA. An association has been confirmed between subclinical atherosclerosis and MetS in RA (Burggraaf et al., 2018), but the evidence is not uniform, and prevalence rates have been quite variable due to geographical heterogeneity and the differing criteria used in the estimation of MetS.

Several previous studies, including two meta-analyses, show a significantly higher prevalence of MetS in established RA compared to control subjects (OR 1.4–1.9) (Abourazzak et al., 2014; Burggraaf et al., 2018; Chung et al., 2008; Crowson et al., 2011; da Cunha et al., 2012; Hallajzadeh et al., 2017; Kerekes et al., 2014; Zhang et al., 2013), with a pooled prevalence of 31% (95% CI: 27.87–33.43) (Hallajzadeh et al., 2017). Some other researchers have reached the opposite conclusion, reporting a higher prevalence of MetS in the healthy controls (Karimi et al., 2011; Mok et al., 2011; Sahebari et al., 2011; Šalamon et al., 2015). There seems to be a difference in the prevalence of MetS among patients with early rheumatoid arthritis (ERA) and those with long-standing disease, although no prospective studies have confirmed an increased risk of MetS development during the course of RA (Kerekes et al., 2014).

The estimated prevalence of MetS in the early stage of the disease has ranged from 16% to 31% in different studies (Kerekes et al., 2014; Kuriya et al., 2019). Recently, an observational study using data from the Canadian Early Arthritis Cohort (CATCH) classified 31% of 1543 ERA subjects as having MetS, according to a modified definition based on routinely collected clinical data (Kuriya et al., 2019).

The metabolic profile observed in patients with RA seems to be different from the MetS mostly associated with obesity in the general population. RA patients tend to have a higher prevalence of abdominal adiposity, hypertension, and altered glucose metabolism, but there is a difference in lipid levels (the “lipid paradox”) and body composition in RA compared to non-inflammatory states. Paradoxically, overweight and obese RA patients appear to carry the lowest CV risk (Kerekes et al., 2014).

A subtype called normal weight metabolically obese – normal-weight individuals with metabolic disturbances (hypertension, hyperglycemia, dyslipidemia) that are characteristic of obesity – has been recognized in the general population and could be even more prevalent in those with RA (Chung et al., 2008; Mathew et al., 2016; St-Onge et al., 2004).

4.4.8. Insulin resistance

Insulin plays a central role in carbohydrate and lipid metabolism (Patel et al., 2016). Early stage glucose intolerance may be compensated for by increased insulin secretion. Insulin resistance (IR) is the term used to describe the inability

of insulin to regulate glucose metabolism due to an inadequate response in peripheral target tissues such as skeletal muscle, adipose tissue, and liver (American Diabetes Association, 2014; Laakso, 2015). IR is not only a matter of deficient glucose uptake, but also a major determinant of CVD risk in nondiabetic individuals (Laakso, 2015).

IR is a long-established predictor of atherosclerosis and coronary artery disease, independent of other risk factors (Després et al., 1996; Patel et al., 2016; Pyöräla, 1979). Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) is a simple and widely used surrogate measure used to detect IR in investigational studies (Matthews et al., 1985). This is an alternative for the reference method for quantifying insulin sensitivity, the euglycemic-hyperinsulinemic glucose clamp method, which is complex and costly (Laakso, 2015). Different cut-off values have been suggested, but there is no universal definition for IR via HOMA-IR values.

Insulin resistance in the general population

A meta-analysis of 65 studies, with a total of 516,325 participants, demonstrated that IR measured by HOMA-IR is associated with a 1.6 times (95% C.I. 1.35, 2.00) increase in the risk of cardiovascular disease in patients without diabetes (Gast et al., 2012). It has been even stated that IR is the most important single cause of coronary artery disease, and in young adults preventing IR could avoid 42% of myocardial infarctions, based on a study using a simulated population representative of young adults in the USA National Health and Nutrition Examination Survey (NHANES) 1998–2004 data (Eddy et al., 2009).

IR is tightly associated with obesity, as well as type 2 diabetes, hypertension, and lipid abnormalities (DeFronzo & Ferrannini, 1991; Nicolau et al., 2017), and plays a central role in the development of metabolic syndrome – one of the most important determinants in the development of CVD (Laakso, 2015; Mottillo et al., 2010; Nicolau et al., 2017).

IR contributes to an enhanced rate of atherosclerosis and cardiovascular risk through multiple pathways, via changes in classic cardiovascular risk factors and downregulating insulin signaling pathways in skeletal muscle, adipose, and liver tissues (Laakso, 2015; Patel et al., 2016). IR in skeletal muscle causes post-prandial hyperglycemia, while in adipose tissue, it increases cytokine and adipokine production, and leads to low-grade inflammation and the development of systemic IR, which contributes to the increased transport of fatty acids to the liver, promoting dyslipidemia (Laakso, 2015). At the same time, over-activation of the sympathetic nervous system induced by IR leads to hypertension and obesity (Laakso, 2015; Patel et al., 2016). IR in endothelial cells leads to impaired vasodilatation and endothelial damage, and at the macrophage level, contributes to atherosclerotic plaque necrosis, instability and enhanced thrombogenesis (Laakso, 2015).

It has been widely established that differences in weight modulate insulin action. Insulin sensitivity declines linearly with BMI, and about 25% of obese subjects in the general population have been reported to be insulin resistant (Abbasi

et al., 2002; Ferrannini et al., 1997). IR in the general population is associated primarily with increasing BMI levels. Adding dual-energy X-Ray absorptiometry (DXA) measured body fat percentage does not add much to the utility of BMI in the prediction of IR, according to NHANES data (Martinez et al., 2017).

Adipose tissue accounts for only 10% of whole-body glucose disposal but has a major role in the development of IR. Hypertrophy of adipose cells leads to the infiltration of immune cells in visceral adipose tissue (but not in subcutaneous deposits) in response to adipocyte hypoxia or apoptosis. Large adipocytes are less sensitive to the anti-lipolytic action of insulin and express higher levels of the proinflammatory chemokines. Ectopic lipid accumulation in other tissues activates local inflammation and lipotoxicity, contributes to organ-specific disease, and exacerbates systemic IR (Laakso & Kuusisto, 2014).

A higher proportion of visceral fat is one of the determinants of the higher risk of CVD induced by IR in men. In men, there is a bidirectional association between low levels of testosterone and central obesity mediated by adipokines through the hypothalamic–pituitary–gonadal axis (Geer & Shen, 2009; Rao et al., 2013).

Additionally, changes in gut microbiota (dysbiosis) in obese subjects promoting systemic inflammation due to gastrointestinal permeability, and an increase in circulating bacterial lipopolysaccharides and DNA, can have a role in the development of IR (Johnson & Olefsky, 2013).

Insulin resistance in rheumatoid arthritis

It is now established from a variety of studies that HOMA-IR levels in rheumatoid subjects are higher than those of population controls, regardless of stratification by demographic or cardiometabolic risk factors (Chung et al., 2008; Giles et al., 2015; Manrique-Arija et al., 2015; Montagna et al., 2007; Nicolau et al., 2017; Shahin et al., 2010).

The prevalence of IR has been found to be 22% (Manrique-Arija et al., 2015) to 73% (Shahin et al., 2010) in early RA and up to 88% in subjects with established disease (Montagna et al., 2007). The presence of IR is associated with inflammatory activity – the level of increase of RA-elevated inflammatory markers (CRP, TNF-alpha, IL-6), high clinical disease activity in both early and longstanding RA, and seropositivity (Gallagher et al., 2019; Giles et al., 2015; Guin et al., 2019; Nicolau et al., 2017; Pamuk et al., 2006).

The fact that increased BMI in the general population leads to a higher risk of disturbed insulin sensitivity is well-known, but interestingly, Giles has reported the largest relative difference between HOMA-IR values in controls and RA patients in the normal weight group, suggesting the importance of other factors involved in the development of IR in RA (Giles et al., 2015).

Glucocorticoids induce IR through the stimulation of hepatic neoglucogenesis, enhanced pancreatic release of insulin, and diminished peripheral insulin sensitivity (Nicolau et al., 2017). Previous research indicates that chronic glucocorticoid therapy is associated with a higher risk of IR (Dessein et al., 2004; Giles et al.,

2015; Nicolau et al., 2017). EULAR recommends weaning patients off glucocorticoids as early as possible to avoid worsening IR and the eventual development of type 2 diabetes (Peters et al., 2010). On the other hand, it has been suggested that the suppression of systemic inflammation through short-term glucocorticoid use may overweigh the detrimental effects of glucocorticoids (Uyl et al., 2012).

Overexpression of TNF-alpha plays a role in the pathophysiology of IR by disrupting the insulin signaling pathway, resulting in reduced insulin sensitivity, the stimulation of adipose tissue lipolysis, and diminished circulating levels of adiponectin (Nicolau et al., 2017). Anti TNF-alpha therapy has been shown to play a beneficial role in reducing IR in rats (Borst, 2004). Men tend to have an enhanced response to inflammatory stimuli through the overproduction of pro-inflammatory cytokines (mainly TNF-alpha, IL-6 and IL-1b) that can decrease androgen production through negative feedback in the hypothalamic–pituitary–gonadal axis and lead to a further risk of IR (Geer & Shen, 2009; Rao et al., 2013).

Using intensive treatment strategies, including TNFalpha targeted treatment, can improve insulin sensitivity (Bissell et al., 2016; Burska et al., 2015; Corrado et al., 2019). A dramatic improvement of insulin and glucose levels has been demonstrated by assessing data prior to and after an intravenous infusion of Infliximab in RA (Gonzalez-Gay et al., 2006). Of the conventional DMARDs, hydroxychloroquine seems to have a beneficial effect on glucose metabolism, independent of inflammation control (Nicolau et al., 2017).

There is a controversy regarding the role of IR in the RA-related CV risk elevation. Although the prevalence of IR is higher in RA patients than in non-RA controls, there is some doubt regarding the role of IR in the development of atherosclerosis in RA. There have been reports of significant association between IR and subclinical atherosclerosis (Guin et al., 2019; Montagna et al., 2007) in RA, but some other researchers have come to the conclusion that higher level of IR may not independently impart additional risk (Chung et al., 2008; Giles et al., 2015; González-Gay et al., 2015). We could not find any long-term observational studies on the topic.

4.4.9. Body composition

Sarcopenia

Loss of muscle mass and function is a natural part of aging. In 1989, Irwin Rosenberg proposed the term “sarcopenia” (Greek “sarx”– flesh+ “penia”– loss) to describe the decrease of muscle mass related to old age (Rosenberg, 1989). Sarcopenia was later defined as the loss of not only skeletal muscle mass, but also a decline in muscle strength and function (dynapenia), associated with a risk of adverse outcomes (Cruz-Jentoft et al., 2010, 2019; Marzetti et al., 2017).

Primary sarcopenia is mainly associated with aging. Age-related sarcopenia is mediated through an altered diet, reduced physical activity worsened by a decreased anabolic response to feeding and exercise, and by chronic low-grade

inflammation with elevated cytokine IL-6 and TNF-alpha levels, a phenomenon known as “inflammaging” (Beaudart et al., 2017; Cruz-Jentoft et al., 2019; Dent et al., 2018; Wilson et al., 2017). The prevalence rates of sarcopenia in the elderly have ranged from 3% to 24%, depending on the diagnostic criteria used (Dent et al., 2018; Tournadre et al., 2018).

Secondary sarcopenia can develop as a consequence of low physical activity, malnutrition, and diseases such as endocrine disorders, malignancy, chronic inflammatory conditions or advanced organ failure (Marzetti et al., 2017).

Sarcopenia is associated with an increased risk of disability, impaired quality of life, higher frequency of falls, osteoporosis, dyslipidemia, cardiovascular risk, metabolic syndrome, immunosuppression and mortality (Cruz-Jentoft et al., 2019; Marzetti et al., 2017).

Dual-energy X-Ray Absorptiometry (DXA) is currently the most widely used method in BC evaluation, enabling a precise and stable quantification of BC, with minimal radiation, separating body lean, fat and bone mass (Marzetti et al., 2017; Shepherd et al., 2017).

There is no universal definition of sarcopenia. Several criteria have been proposed, based on the muscle quantity, muscle strength, and/or physical performance (muscle quality). Muscle quantity can be reported by appendicular lean mass (ALM)- the combined muscle mass of hands and legs. As muscle mass is correlated with body size (individuals with a larger body size have larger lean mass), when quantifying muscle mass, lean mass can be adjusted for body size using height squared (ALM/height^2), weight (ALM/weight) or body mass index (ALM/BMI), with no clear advantage of any of the methods (Cruz-Jentoft et al., 2019).

In 2019, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed a scheme for the detection of sarcopenia, taking into account muscle quantity, muscle strength and performance (Cruz-Jentoft et al., 2019). The implementation of these criteria has not been tested in subjects with RA. Measures of muscle strength and performance (e.g., grip strength) in patients with RA can be affected by various patient-related factors, such as pain, arthritis activity, deformities, and disability resulting in values lower than in healthy individuals, and representing burden of the disease more than muscle quality (Higgins et al., 2018; Uutela et al., 2018). On the other hand, using EWGSOP criteria can lead to an underestimation of sarcopenia in the general population. Avoiding this through diagnosing sarcopenia by appendicular lean mass adjusted to height value alone has been recently suggested (Dawson-Hughes & Bischoff-Ferrari, 2016).

Sarcopenic obesity and insulin resistance

Sarcopenic obesity – the co-occurrence of obesity and sarcopenia – seems to be associated with higher risk for adverse effects than either of its components alone (Tournadre et al., 2018). Obesity exacerbates sarcopenia through the infiltration

of fat into muscle, reducing physical function and increasing the risk of mortality (Cruz-Jentoft et al., 2019).

In sarcopenic obesity, lean mass loss is accompanied not only by a gain in visceral fat, but also fat infiltration in skeletal muscle (myosteatosis) with an accumulation of toxic lipids – ceramides and triglycerides (Hong & Choi, 2020; Kalyani et al., 2014; Tournadre et al., 2018).

Skeletal muscle is the largest insulin-sensitive tissue, and has the highest glucose requirements, accounting for up to 80% of glucose uptake during hyperinsulinemia (Laakso & Kuusisto, 2014). An inverse relationship between skeletal muscle mass and IR has been reported in the general population (Cleasby et al., 2016; Srikanthan et al., 2010; Srikanthan & Karlamangla, 2011). In sarcopenic obesity, insulin-stimulated glucose disposal in skeletal muscle is markedly impaired, leading to catabolic status and skeletal muscle atrophy (Hong & Choi, 2020). Sarcopenic obesity is associated with more severe functional decline and outcomes than either condition alone (Cleasby et al., 2016; Kalyani et al., 2014; Tournadre et al., 2018).

Body composition in rheumatoid arthritis

The phenomenon known as "rheumatoid cachexia" was first described by Sir James Paget, who wrote: "... wasting occurs, in greater or lesser degree, in all muscles near joints that are inflamed... It is, I repeat, not a mere wasting from disuse: it is far more rapid that that..." in the Lancet in 1873 (Paget, 1873). The term "cachexia" was defined in 2008 as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass" (Evans et al., 2008). Nowadays, the prominent feature of classic cachexia – weight loss – is rare in RA, although it's sometimes seen in severe longstanding untreated arthritis (Summers et al., 2010).

While in sarcopenia related to aging, a parallel loss of fat mass appears and total body mass declines (Kalyani et al., 2014), sarcopenia in RA usually develops without a change in body mass (Summers et al., 2010). An abnormal body composition appears with loss of muscle and concomitant fat mass preservation or accumulation (Challal et al., 2015; Summers et al., 2010). Due to the change in body composition (BC) at the same BMI and weight, patients with RA have significantly lower lean mass compared to the healthy population, making this form of cachexia difficult to recognize by clinical examination alone. To date, there is no accepted operational definition for rheumatoid cachexia.

Evidence of muscle wasting (sarcopenia) and fat mass gain (overfat) without a change in body weight, known as sarcopenic obesity or rheumatoid cachexia, has been reported in up to two thirds of RA patients with established disease (Challal et al., 2015; Rall & Roubenoff, 2004; Roubenoff, 2009; Roubenoff et al., 1992; Summers et al., 2010). In a recent meta-analysis, the prevalence of rheumatoid cachexia was found to be 15–32% depending on the criteria used (Santo et al., 2018).

Contrary to the general population, an inverse relationship between BMI and risk of death in RA has been found, phenomenon known as the "obesity paradox." Obesity in RA protects against cardiovascular mortality and weight loss is associated with elevated CV risk (Baker et al., 2015; England, Baker, et al., 2018). To date, no studies have directly evaluated the role of altered BC in CV mortality in RA. Findings by Delgado Frias and his colleagues suggest that sarcopenia in RA is associated with endothelial dysfunction (reduced brachial artery flow-mediated dilatation), possibly leading to a higher cardiovascular risk (Delgado-Frías et al., 2015).

Factors affecting body composition in rheumatoid arthritis

In 1992, Roubenoff first reported that rheumatoid cachexia is associated with mediators of inflammation (Roubenoff et al., 1992). The loss of muscle tissue in RA seems to be mediated through pro-inflammatory sarcoactive cytokines, including TNF-alpha, IL-1, and IL-6, which induce proteolysis (Engvall et al., 2008; Tournadre et al., 2018).

The long-term effect of glucocorticosteroids – potent anti-inflammatory medications leading to muscle wasting, fat accumulation, and fat redistribution – is a well-known phenomenon (Buttgereit & Burmester, 2016; Cutolo et al., 2014).

Interestingly, when using tightly controlled therapy (a treat-to-target approach) (Lemmey et al., 2016) or biological treatment, even if started early (S. M. Marcora et al., 2006; Marouen et al., 2017), disease activity decreases, but the loss of lean mass is resistant to change. TNF-alpha targeting therapy could lead to further worsening of BC due to a gain in fat mass (Tournadre et al., 2018). Regarding the effect of IL-6 inhibitors, in one study, a beneficial effect to lean mass was reported without a gain in fat tissue, possibly through an effect mediated by leptin modulation (Tournadre et al., 2017).

Some authors have found unfavorable BC to already be evident in the initial stage of RA, potentially mediated by preclinical immunologic events (Giles, 2019). There is no general agreement for which factors contribute to this change (Book et al., 2009, 2011; Dao et al., 2011; Giles, 2019; S. M. Marcora et al., 2006).

A Swedish group reported that ERA patients with a mean disease duration of 7 months had lower lean mass, but only women with RA were found to have a higher fat mass compared to controls. Lean mass reduction was associated with advanced age, but no association was found with disease specific measures (Book et al., 2009). After two years of routine care (including DMARD treatment and rehabilitation), the same researchers found that further decrease in lean mass and increase in truncal fat was lower in the RA group compared to control subjects, showing that the change could be potentially modifiable (Book et al., 2011).

A higher prevalence of altered BC has been reported by a Vietnamese group focusing on women with RA (with a mean disease duration of 22 months) compared to matched controls. In this group, a change in BC was associated with RA activity and disability, and a lower frequency of regular exercise in sarcopenic

subjects. Additionally, the role of glucocorticoid usage (68% of the patients were taking GCS) was evaluated, but no associations were found with either fat nor lean mass measures (Dao et al., 2011). In neither of the groups studied were treatment naïve RA patients.

BC in early arthritis patients with no previous DMARD treatment was evaluated in a study by Turk et al, which found that loss of muscle mass was 4–5 times more common in patients with arthritis than controls, but no associations between disease activity and an unfavorable BC were found (Turk et al., 2018). In previous studies, the role of lifestyle in association with lean mass parameters has rarely been assessed.

A healthy diet, especially with sufficient protein intake, is essential for the prevention of age-related loss of muscle mass, so protein supplementation is recommended for treating age-related sarcopenia (Beaudart et al., 2017; Dent et al., 2018; Geirsdottir et al., 2013; Tournadre et al., 2018). Sarcopenia in RA is believed to develop without changes in diet (Engvall et al., 2008; Rall & Roubenoff, 2004). It has been reported that up to 75% of RA patients believe food plays an important role in their symptom severity but the role of diet is less accepted by physicians in the management of RA (Cutolo & Nikiphorou, 2018; Stamp et al., 2005). Most researchers studying BC change in RA have not looked very closely into nutrition. The role of protein supplementation (a mixture of β-hydroxy-β-methyl-butyrate, glutamine and arginine) has been evaluated in established rheumatoid cachexia but found to be no different than placebo in a short term interventional study (S. Marcora et al., 2005). We could only find one study where the role of diet in BC change in RA was evaluated, but no associations between calorie or protein intake and muscle parameters were found (Barone et al., 2018).

The cornerstone in the prevention of age related muscle loss is sufficient physical activity (Beaudart et al., 2017; Dent et al., 2018). RA patients tend to be physically inactive due to arthralgia, fatigue and stiffness (Sokka T. et al., 2008). High intensity resistance training has been shown to improve the outcome of RA, including BC (Lemmey et al., 2009, 2009), but these exercise programs are often difficult to implement due to low adherence (especially for long-term intervention) (Tournadre et al., 2018). Sarcopenia has a significant impact on quality of life. Patients with RA and sarcopenia have a lower quality of life, with health assessment questionnaire disability index (HAQ-DI) scores 0.25 units higher on average, than those without sarcopenia (Giles, Bartlett, et al., 2008). A recent review estimated that the yearly direct medical expenditure due to the impact of sarcopenia on disability would be $562 million for the 169,000 US patients with RA who were estimated to be sarcopenic, and concluded that finding a pre-RA intervention able to prevent or reduce the development of sarcopenia would result inconsiderable improvement in physical function and quality of life, and direct and indirect cost savings (Giles, 2019).

5. STUDY RATIONALE

RA is still associated with an elevated risk of cardiovascular disease, and the resulting premature morbidity, despite the fact that the course of RA has become milder due to tight control and aggressive treatment strategies.

The excess CVD risk associated with RA is only partly explained by traditional cardiovascular risk factors and inflammatory burdens. Established RA is associated with a higher prevalence of cardiometabolic risk factors, but less is known about the time of onset of these changes. Cardiovascular mortality has been found to be increased in even early RA, leading to a hypothesis that the alterations in cardiometabolic risk profile develop in the earliest phase of the disease.

The risk of RA-related CVD is highest in patients with normal body mass for reasons not yet fully understood. Patients with higher weight status seem to have a lower risk for premature CV mortality – the opposite of what has been found in the general population.

In addition to increased CVD mortality in normal weight patients with RA, there seems to be a higher prevalence of cardiometabolic risk factors not predictable by weight status. Therefore, we aimed to test the hypothesis that the presence of metabolic disturbances in normal weight individuals (metabolic obesity) is already present in the early stage of the disease.

An increasingly frequent cardiometabolic risk factor traditionally associated with obesity, insulin resistance has been found to be present in a majority of patients with established RA. Prevalence reports in early RA have been rather inconsistent, ranging from 1/5 to 3/4 of studied subjects, so we decided to analyze this in the Estonian cohort of early RA.

Little is known about the associations between body composition and IR in RA. In established RA, the largest relative difference between the insulin sensitivity of controls and patients has been found in the normal weight group, suggesting the importance of factors other than obesity in the development of IR in RA. It is well known that excess fat is associated with reduced insulin sensitivity, but the majority of glucose disposal takes place in lean tissue, supporting the hypothesis that altered BC may have a role in the development of IR in RA. Previous studies in the field have been limited to reports of associations between BMI and IR in RA without detailed analysis of the role of body composition in reduced insulin sensitivity. This thesis aims to address that gap in knowledge.

It is known that in the course of RA, alterations of body composition appear, with a decline in lean mass and an increase in fat mass, but it is not clear if these changes develop in the preclinical, early stage of RA or later in the course of the disease. We could find only a couple studies looking at factors associated with body composition in early RA, most taking into account only directly disease-associated features, such as disease activity and inflammatory markers, with mixed results. From the vast data available on aging-related sarcopenia, it is clear that chronic inflammation is important in the process, but so are nutrition and physical

activity. RA is accompanied by a lack of physical activity due to pain, stiffness and fatigue; it is clear that lifestyle factors should be taken into account as well when analyzing BC in RA. As muscle loss in established RA seems to be irreversible, it is vital to find the factors contributing to the change in the earliest stage of the disease to avoid a decrease in quality of life and premature cardiovascular mortality. We could not find any published studies where both disease associated factors and the role of lifestyle were analyzed in early RA.

6. AIMS OF THE THESIS:

The general aim of this study was to evaluate cardiometabolic risk factors in early rheumatoid arthritis.

This work is focused on body compositional parameters and associations with metabolic factors in patients with early rheumatoid arthritis compared to population controls.

Specific aims were:

1. to evaluate the cardiometabolic risk profile in early rheumatoid arthritis by assessing the presence and components of metabolic syndrome (Paper I) and the prevalence of insulin resistance (Paper II)
2. to find the factors associated with insulin resistance in early rheumatoid arthritis (Paper II)
3. to assess the body composition of early rheumatoid arthritis patients at disease onset compared to population controls (Paper III)
4. to examine the associations between arthritis disease specific features, physical activity, nutritional factors and body composition in early rheumatoid arthritis (Paper III)

7. SUBJECTS AND METHODS:

7.1. Subjects

7.1.1. Early rheumatoid arthritis group

The thesis is based on a cross-sectional study of 92 patients with ERA. To form the study group, 100 consecutive patients referred to Tartu University Hospital from January 2012 to May 2014 with a first-ever RA diagnosis and symptom duration of up to one year (early arthritis) were invited to participate in the study. To be included in the study, the ACR/ EULAR 2012 classification criteria for RA (Aletaha et al., 2010) had to be fulfilled. Two patients with other inflammatory joint conditions were excluded (one had ankylosing spondylitis, one arthritis associated with HCV diagnosed in follow-up). One patient with achondroplasia was excluded from data analysis in Paper III due to altered body proportions and one patient was excluded from Paper II due to extremely high insulin levels (140.9 mU/l).

No patients in the RA group had concomitant pulmonary conditions, heart failure or malignancy considered clinically important by the investigator, although one case had treated ovarian cancer in their medical history.

7.1.2. Population- based comparison group (Papers II, III)

350 subjects adjusted for the age and gender composition of the Estonian population in 2013 were randomly selected from a primary health care center practice list (the total number of subjects was 1854). First, postal invitations with introductory materials were sent out. A total number of 332 subjects contacted the primary health care center for further instruction and were recruited during the study period (September 2014–April 2015). Three subjects missed their study appointment, eight were excluded due to missing outcome data (seven subjects with missing insulin values were excluded from data analysis in Paper II, and one subject with no BC data from Papers II, III). The final number of control subjects in Paper II: 321, and 328 in Paper III.

7.1.3. Matched controls (Paper I)

The control group consisted of 273 individually age- (+/– 3 years) and sex-matched random subjects, selected from a previous population-based cross-sectional multicentric study conducted between November 2008 and May 2009 in three different Estonian counties (Eglit et al., 2012, 2013). The study population consisted of randomly selected adults aged 20–74 years from four primary care center practice lists. The initial study population was selected to be representative

of the general Estonian population in terms of age and gender. Three controls per 1 early RA case were selected (1:3 ratio).

All subjects participating in the study signed written informed consent forms. The study was approved by the Research Ethics Committee of the University of Tartu (approval no.

232/M-13, date of approval 03.10.2011; approval no 238/M-15, date of approval 16.06.2014)

7.2. Methods

7.2.1. Medical interview

A face-to-face medical interview was conducted, information on first symptoms of arthritis (pain, swelling) was collected, and the onset of patient reported joint swelling was considered to be the first definite symptom of RA. The presence of concomitant health conditions, including diabetes, cardiovascular disease, and treatment with antirheumatic (NSAID, GCS, DMARD), antihypertensive and lipid lowering medications was assessed. The time of the first diagnosis of RA was confirmed using data in electronical health records and fulfillment of ACR/ EULAR 2010 criteria for classification (Aletaha et al., 2010) was evaluated retrospectively.

7.2.2. Physical examination

A standardized physical examination was performed. In the RA group, tender and swollen joint counts (28 and 42 joint scores) were performed by a certified rheumatologist. Body weight was measured in kilograms with an electronic scale, subjects wore light indoor clothing without shoes. Height was measured to the nearest 0.5 cm using a stadiometer. Waist circumference was measured midway between the lower rib margin and the iliac crest. Blood pressure was measured after five minutes of sitting with a calibrated sphygmomanometer.

7.2.3. Patient reported outcomes

The quality of life of RA patients was assessed using the standardized Health Assessment Questionnaire Disability Index (HAQ-DI) questionnaire, and global health was assessed using visual analogue scale (0–100mm).

Physical activity was measured using the International Physical Activity (IPAQ) short form (The IPAQ group, 2003). At least 150 minutes of moderate – or 75 minutes of vigorous – physical activity throughout the week was considered to be sufficient as recommended by the WHO (WHO, 2010).

A 24-hour dietary recall (24HDR) capturing information about foods and beverages consumed over the past 24 hours was used to evaluate energy and nutrient intake. The 24HDR data was entered into the NutriData software created by the Estonian National Institute for Health Development to translate foods and beverages in the Estonian food composition database into nutrient equivalents (National Institute for Health Development, n.d.).

7.2.4. Blood samples

Blood samples were collected between 8 a.m. and 11 a.m. after an overnight fast.

Glucose (hexokinase assay), ESR (Westergren method), CRP (immunoturbidimetric method), total cholesterol, HDL-cholesterol, and triglycerides were measured (enzymatic colorimetric assay) according to standard methodology in a local laboratory (United Laboratories of Tartu University Hospital). Seropositivity for ACPA and RF was evaluated in the RA group. ACPA was measured using electrochemiluminescence assay, using the value of 17k U/L as the cut-off for positivity. To measure RF, the immunoturbidimetric method was used and the test was considered positive if the RF value was >14 IU/mL.

Serum was separated from peripheral venous blood samples, stored at –80 C until analysis and a panel of metabolic markers, including IL-6, TNF-alpha, and insulin was evaluated using Luminex xMAP® technology (Luminex Corp).

7.2.5. RA disease activity assessment

The Disease Activity Score (DAS 28) was calculated according to the standard formula, using 28 joint scores, patient global health assessment, and ESR (Papers II, III) or CRP values (Paper I) (van Gestel et al., 1998). The patients were grouped according to their DAS 28 scores as having remission (DAS 28 score <2.6), low disease activity (DAS 28 score <3.2), moderate disease activity (≥3.2 to ≃5.1) or high disease activity (>5.1).

7.2.6. Cardiometabolic risk profile assessment

Metabolic syndrome

To diagnose MetS, the NCEP ATP III criteria (Grundy et al., 2004; "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report," 2002) were used: the syndrome was present if at least three of the following criteria were observed: abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia or low HDL.

The presence of abdominal obesity was defined by waist circumference ≥102 cm in men and ≥88 cm in women. The subject had hypertension if blood

pressure was ≥130/85 mmHg or they were taking antihypertensive medication. Hyperglycemia was defined by having fasting glucose: ≥5.6 mmol/L or previously diagnosed diabetes. Hypertriglyceridemia was confirmed if TG value was ≥1.7 mmol/L or the subject was taking lipid-regulating medication; low HDL was defined as having HDL cholesterol <1.03 mmol/L in men and <1.30 mmol/L in women, or if the patient was currently on drug treatment for reduced HDL.

Normal weight subjects with metabolic syndrome were classified as normal weight metabolically obese.

Insulin resistance

Homeostatic model assessment of IR (HOMA-IR) was calculated according to the following formula: fasting insulin (mU/L) x fasting glucose (mmol/L)/22.5 (Matthews et al., 1985). The cut-off value defined for IR was the 75th percentile of the population-based comparison group values.

7.2.7. Body composition

Definition of weight status

BMI was calculated according to the standard formula – weight in kg divided by height in meters squared. BMI groups were formed – normal weight (BMI ≤ 24.9 kg/m^2), overweight (BMI 25–29.9kg/m^2), and obese (BMI ≥30 kg/m^2), according to the WHO criteria (WHO, 2010).

Quantification of muscle and fat mass

Total and regional (left and right arm, left and right leg, trunk, head) BC parameters were assessed with a Lunar Prodigy Advance Dual Energy X-Ray absorptiometry (DXA) machine for the RA group and the population-based comparison group. Fat mass, fat free and muscle (lean) mass were measured. Appendicular lean mass was calculated as the sum of lean mass of hands and legs. Body fat and lean mass indices were calculated.

In Paper II, FMI: fat mass index (fat mass kg/height squared); FFM: fat-free mass; FFMI: fat-free mass index (fat-free mass/height squared); ALM: appendicular lean mass; ALMI: appendicular lean mass index (appendicular lean mass kg/BMI) were calculated. FMI and ALMI were used to assess the role of body compositional parameters associated with the presence of insulin resistance.

In Paper III, body fat percentage (BFP, the fat percentage of total body mass), and the appendicular lean mass index ALM/h^2 (appendicular lean mass/height squared) were calculated. As there is no universal definition for low lean mass in RA, we set the cut-off point as having an ALM/h^2 less than the 20th percentile of

the sex-specific population-based comparison group values (Paper III), corresponding to a threshold value of 8.0586 kg/h^2 for males, and 6.0359 kg/h^2 for females. Overfat was defined as BFP >25% for men and >35% for women (WHO, 1997). Using these cut-off values, BC phenotypes were defined: overfat, low lean mass, overfat with low lean mass. A subject was classified as having healthy BC if both lean and fat mass were within normal values.

7.2.8. Statistical analysis

Statistical analysis was performed using SPSS v. 22–24 (IBM Corp., USA). Two-tailed tests and a 5% significance level with Bonferroni correction for multiple comparisons were used in all analyses.

Methods of descriptive statistics as means and standard deviations were used for continuous variables, categorical variables were presented in counts and percentages.

Odds Ratios (OR), the Chi-square test, and Fisher's exact test were used to compare frequencies of categorical variables. Student's T-test for normally distributed data, and the Mann-Whitney U test for non-parametric data, were used to compare means.

Binomial logistic regression was performed to ascertain the effects of subject characteristics on the likelihood of being classified as insulin resistant (Paper II), the effects of age and gender adjusted subject characteristics on the likelihood of low lean mass and the associations between ERA and BC phenotypes (Paper III). The linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure.

8. RESULTS

8.1. Demographic and clinical laboratory characteristics

Mean age in the RA group was 52 years (19–77), 72% were female, and male patients were slightly older (55±3 years) than females (52±2 years).

The majority of RA patients were seropositive for ACPA (88%) and/or RF (88%). The mean time elapsed from the onset of self-reported synovitis was 201±58 days, and the mean time from diagnosis was 26.8±10.3 days.

Most of the patients had active disease – approximately 30% had high, 40% moderate and 30% low disease activity (classified according to the ACR recommendations (Anderson et al., 2012)). Mean DAS28 score was 4.8±0.3, mean ESR was 20.3±2.3 mm/h, and CRP 12.3±2.0 g/l, mean swollen joint count 4.8±0.6 and tender joint count 10.6±0.9.

Male RA patients had higher disease activity, higher levels of inflammatory markers, and a higher proportion of ACPA and RF seropositivity compared to women.

More than half of the subjects (56%) had started DMARD therapy by the time of the study visit, about one fourth (28%) were on glucocorticoid treatment, with a mean dosage of 13.8±1.2mg prednisolone a day.

Characteristics of the matched controls (Paper I): 273 subjects participating in the study as matched controls were age/gender matched to patients in the early RA group. The mean age of the subjects was 51.5±2 years, 72.5% were female.

Characteristics of the population-based comparison group (Papers II, III): The mean age of the group was 48±1years, 54% of the subjects were female. There was a statistically significant difference between demographics (age, gender) in the control and early RA group. There were more women in the RA group, and subjects in the control group were younger ($p<0.05$).

8.2. Cardiometabolic risk profile

8.2.1. Metabolic syndrome

Components of metabolic syndrome in patients with early RA and matched controls (Paper I)

There was no statistically significant difference between the early RA and age/gender matched control group in mean BMI values or the presence of MetS – 35.2% of the ERA subjects were classified as having MetS, as were 34.1% of the controls (Table 1).

Patients with early RA had higher mean systolic and diastolic blood pressure values than controls. 72.5% of the early RA patients and 61.2% of the controls were classified as having hypertension. Looking at the proportion of subjects with

treated hypertension, we found that only 30.8% RA patients received anti-hypertensive treatment compared to the majority – 52.6% of the control subjects with elevated blood pressure.

There was no difference in the prevalence of abdominal obesity, hyperglycemia, or dyslipidemia between the two groups.

Table 1. Cardiometabolic risk factors in early RA group and control subjects

	Early RA N= 91	**Control group N= 273**	**OR (95% CI)**	***p***
BMI (kg/h^2)	27.1 (5.6)	28.2 (6.3)		NS
Normal weight N (%)	36 (40.0%)	88 (32.6%)	1.4 (0.8, 2.2)	NS
Overweight N (%)	31 (34.4%)	86 (31.9%)	1.1 (0.7, 1.9)	NS
Obese N (%)	23 (25.6%)	96 (35.6%)	0.6 (0.4, 1.1)	NS
Metabolic syndrome N (%)	32 (35.2%)	93 (34.1%)	1.0 (0.6, 1.7)	NS
Systolic blood pressure (mmHg)	137 (22)	131 (19)		0.01
Diastolic blood pressure (mmHg)	85 (12)	81 (10)		<0.01
Hypertension N (%)	66 (72.5%)	167 (61.2%)	1.7 (0.9, 2.8)	0.05
Waist circumference (cm)	90 (13)	92 (16)		NS
Abdominal obesity N (%)	43 (47.3%)	133 (48.7%)	0.9 (0.6, 1.5)	NS
Fasting glucose (mmol/l)	5.3 (0.7)	5.4 (0.8)		NS
Hyperglycemia N (%)	28 (30.8%)	87 (31.9%)	0.9 (0.6, 1.5)	NS
HDL cholesterol (mmol/l)	1.6 (0.5)	1.6 (0.5)		NS
Low HDL N (%)	23 (25.3%)	67 (24.5%)	1.0 (0.6, 1.6)	NS
Triglycerides (mmol/l)	1.2 (0.6)	1.3 (0.7)		NS
High TG N (%)	21 (23.1%)	64 (23.4%)	0.9 (0.5, 1.6)	NS

Mean, ± SD unless otherwise stated. Statistically significant differences $p < 0.05$. TG – triglycerides, HDL – high density lipoprotein, NS – non-significant

Note: Adapted from Müller R et al. The metabolic profile in early rheumatoid arthritis: a high prevalence of metabolic obesity. Rheumatol Int. 2017 Jan;37(1):21–27. Springer-Verlag Berlin Heidelberg

Among the RA group, we found no difference between patients with and without MetS in the disease activity parameters (DAS 28 value, swollen, tender joint count, SR, and CRP), disease duration, NSAID, or glucocorticoid treatment.

Components of metabolic syndrome by weight status

Components of MetS in normal and obese subjects are shown in Table 2. When looking into the data of normal weight subjects, the odds of being classified as metabolically obese were 5.6 times higher for early RA subjects compared to controls. Of the individual components of metabolic syndrome normal weight RA subjects had higher odds of having hypertension (OR 2.8) and hyperglycemia (OR 2.9) compared to controls. In this group, the proportion of both RA patients and controls with hypertension and receiving antihypertensive medication was low – 17% of RA patients and 33% of the control subjects were treated.

As expected, almost half of the overweight/obese subjects had MetS. The prevalence of MetS and all of its components (hypertension, abdominal obesity, low HDL, high TG and hyperglycemia) was higher among overweight/obese subjects in both groups, without a significant difference between early RA and control subjects.

Table 2. Prevalence of metabolic syndrome and metabolic risk factors in normal-weight and overweight sub-groups of early RA subjects and the control group

	Normal weight			**Overweight/obese**		
	Early RA N=36	**Control group N= 88**	**OR (95%CI)**	**Early RA N=55**	**Control group N=185**	**OR (95%CI)**
Metabolic syndrome	**6 (16.7)**	**2 (2.3)**	**5.6 (1.3, 23.8)**	26 (47.3)	91 (49.2)	0.9 (0.5, 1.7)
Hypertension	**21 (58.3)**	**27 (30.7)**	**2.8 (1.3, 6.0)**	45 (81.8)	137 (74.1)	1.6 (0.7, 3.3)
Abdominal obesity	3 (8.3)	2 (2.3)	3.9 (0.6, 24.2)	40 (72.7)	131 (70.8)	1.1 (0.6, 2.3)
Low HDL	4 (11.1)	11 (12.5)	0.7 (0.2, 2.4)	19 (34.5)	56 (30.3)	1.2 (0.6, 2.2)
High TG level	6 (16.7)	10 (11.4)	1.5 (0.5, 4.6)	15 (27.3)	54 (29.2)	0.9 (0.4, 1.7)
Hyperglycemia	**9 (25.0)**	**8 (9.1)**	**2.9 (1.0, 8.0)**	19 (34.5)	79 (42.7)	0.7 (0.4, 1.4)

N (%) Statistically significant differences shown in boldface type (p <0.05). TG – triglycerides, HDL – high density lipoprotein

Note: Adapted from Müller R et al. The metabolic profile in early rheumatoid arthritis: a high prevalence of metabolic obesity. Rheumatol Int. 2017 Jan;37(1):21–27. Springer-Verlag Berlin Heidelberg

8.2.2. Insulin resistance

Insulin resistance in the RA and population-based comparison groups (Paper II)

There was no difference in glucose values between the early RA and control group. The patients with ERA had significantly higher mean insulin values, higher HOMA-IR scores; and a higher proportion of insulin resistance – 55% of the ERA patients were classified as being insulin resistant, compared to 25% of the control subjects (Table 3.).

Male subjects were more likely to be classified as insulin resistant than females.73% of the males in RA group were insulin resistant, compared to 28% among the controls.

Table 3. Insulin sensitivity in early RA subjects and control group

	Gender					
	Male		**Female**		**Total**	
	Early RA N= 26	**Control group N= 148**	**Early RA N= 66**	**Control group N= 173**	**Early RA N= 92**	**Control group N= 321**
Glucose (mmol/l)	5.3 (0.1)	5.4 (0.1)	5.3 (0.1)	5.2 (0.1)	5.3 (0.1)	5.3 (0.0)
Insulin (mU/l)	**15.3 (1.9)**	**7.2 (0.4)**	**13.2 (2.2)**	**6.9 (0.4)**	**13.8 (1.6)**	**7.0 (0.3)**
HOMA-IR score (units)	**3.6 (0.4)**	**1.8 (0.1)**	**3.1 (0.5)**	**1.7 (0.1)**	**3.2 (0.4)**	**1.7 (0.1)**
Insulin resistant N (%)	**19 (73.1)**	**41 (27.7)**	**32 (48.5)**	**39 (22.5)**	**51 (55.4)**	**80 (24.9)**

Values are the mean, ± S.E. if not stated otherwise. Statistically significant differences shown in boldface type (p <0.05). HOMA-IR – homeostatic model assessment for insulin resistance,
Note: Adapted from Müller R, et al. Insulin Resistance in Early Rheumatoid Arthritis Is Associated with Low Appendicular Lean Mass. Biomed Res Int. 2017;2017:9584720 (licensed under Creative Commons)

Factors associated with insulin resistance (Paper II)

Looking into the unadjusted characteristics of IR and non-IR RA patients, those classified as being insulin resistant had higher inflammatory markers (CRP, TNF-alpha, and IL-6) and higher disease activity (Table 4). The mean DAS 28 score in the non-IR group was 3.6±0.2, and 4.6±0.2 in the IR group. 43% of the insulin-resistant patients had high disease activity compared to 12% of the non-insulin resistant group.

Table 4. Characteristics of non-insulin resistant and insulin resistant early RA patients

	Non-insulin resistant N=41	Insulin resistant N=51	*p*
Age (years)	51 (2)	54 (2)	NS
Male gender N (%)	7 (17.1)	19 (37.3)	0.02
BMI (kg/h^2)	26.3 (0.8)	27.9 (0.9)	NS
CRP (mg/l)	8.6 (3.0)	14.5 (2.4)	0.01
TNF-alpha (pg/ml)	2.1 (0.1)	3.4 (0.4)	0.001
IL-6 (pg/ml)	8.6 (4.2)	23.2 (5.3)	<0.001
RF positive N (%)	25 (61.0)	39 (76.5)	NS
ACPA positive N (%)	25 (61.0)	38 (74.5)	NS
DAS28 score (units)	3.6 (0.2)	4.6 (0.2)	0.003
Low disease activity N (%)	18 (45.0)	11 (21.6)	0.02
Moderate disease activity N (%)	18 (43.9)	18 (35.3)	NS
High disease activity N (%)	5 (12.2)	22 (43.1)	0.001
Current GCS usage N (%)	10 (25.0)	16 (31.4)	NS
Current DMARD usage N (%)	24 (58.5)	27 (52.9)	NS
Disease duration (days)	234.7 (37.5)	199.5 (32.3)	NS
Total fat mass (kg)	26.2 (1.7)	28.1 (1.6)	NS
FMI (kg/h^2)	9.5 (0.6)	10.6 (0.7)	NS
ALM (kg)	18.7 (0.6)	19.3 (0.6)	NS
ALMI (kg/BMI)	0.73 (0.03)	0.72 (0.03)	NS

Mean, ± S.E. if not stated otherwise, statistically significant differences $p < 0.05$. BMI – body mass index, CRP – C-reactive protein, TNF-alpha – tumor necrosis factor alpha, IL-6 – interleukin 6, RF-rheumatoid factor, DAS28 – disease activity score calculated using 28 joints, GCS – glucocorticosteroid, FMI – fat mass index (fat mass kg/ height h^2), ALM – appendicular lean mass, ALMI – appendicular lean mass index (appendicular lean mass kg/BMI), NS – non-significant

Note: Adapted from Müller R et al. Insulin Resistance in Early Rheumatoid Arthritis Is Associated with Low Appendicular Lean Mass. Biomed Res Int. 2017;2017:9584720 (licensed under Creative Commons)

The presence of IR was independently associated with gender, RA group, FMI, and ALMI (according to binomial logistic regression). Early RA patients had 4.8 times higher odds of being classified as insulin resistant¸ and males had 7.7 times higher odds of exhibiting insulin resistance than females (Table 5).

Table 5. The effects of age, gender, body composition indices and having early RA, on the likelihood of IR

	B	± S.E.	OR	95% CI	*p*
RA group	1.57	0.31	4.80	2.61, 8.82	<0.001
Male gender	2.04	0.54	7.70	2.69, 22.08	<0.001
Age group <29	0.53	0.44	1.69	0.71, 4.0	NS
Age group 30–49	–0.22	0.31	0.80	0.44, 1.47	NS
FMI	0.20	0.06	1.21	1.08, 1.38	0.002
FFMI	0.07	0.08	1.08	0.92, 1.27	NS
ALMI	–3.02	1.57	0.05	0.002, 1.06	0.05

Statistically significant differences $p < 0.05$. Age groups <29 and 30–49 compared to >50. FMI – fat mass index (fat mass kg/ height h^2), FFMI – fat-free mass index (fat-free mass/ height m^2), ALMI – appendicular lean mass index (appendicular lean mass kg/BMI), NS – non-significant
Note: Adapted from Müller R, et al. Insulin Resistance in Early Rheumatoid Arthritis Is Associated with Low Appendicular Lean Mass. Biomed Res Int. 2017;2017:9584720 (licensed under Creative Commons)

Using binomial logistic regression to determine the variables associated with IR in the ERA group, we found that men had 7.4 times higher odds of being insulin resistant than females, and patients with high disease activity had 6.2 times higher odds of having IR than those with low disease activity. Lower ALMI was associated with an increased likelihood of IR (Table 6).

Table 6. Summary of binary logistic regression analysis for variables predicting insulin resistance in the early RA group

	B	± S.E.	OR	95% CI	*p*
Male gender	2.0	0.80	7.35	1.55, 34.91	0.01
ALMI	–3.45	1.74	0.03	0.001, 0.97	0.05
TNF-alpha (pg/ml)	0.42	0.26	1.52	0.91, 2.53	NS
High DAS 28 score	1.82	0.65	6.19	1.72, 22.2	0.005
Moderate DAS28 score	0.48	0.53	1.62	0.57, 4.59	NS

Statistically significant differences $p < 0.05$. ALMI – appendicular lean mass index (appendicular lean mass kg/BMI), TNF-alpha – tumor necrosis factors alpha, DAS 28 – disease activity score based on 28 joints, NS – non-significant
Note: Adapted from Müller R et al. Insulin Resistance in Early Rheumatoid Arthritis Is Associated with Low Appendicular Lean Mass. Biomed Res Int. 2017;2017:9584720 (licensed under Creative Commons)

8.2.3. Body composition

Body composition in RA patients and controls (Papers II and III)

There was no difference in BMI values between the matched controls and ERA group (Paper I).

There were more men among the population-based comparison group (Papers II and III), resulting in a taller and heavier group, but there was no difference in the mean BMI values or prevalence of overweight or obesity between the groups.

Of the BC parameters, patients with ERA had lower muscle indices – lower fat-free, appendicular lean mass and appendicular lean mass adjusted for body size (ALM/BMI or ALM/h^2) as shown in Table 7. There was no difference between unadjusted body fat values between the groups.

Table 7. Body composition in early RA patients and controls

			Male			Female		
	Early RA N=91	**Control Group N = 328**	***p***	**Early RA N= 25**	**Control Group N = 151**	***p***	**Early RA N= 66**	**Control Group N = 171**	***p***
Fat mass (kg)	27.3 (1.1)	26.5 (0.6)	NS	22.5 (1.9)	24.1 (0.9)	NS	29.2 (1.3)	28.5 (0.9)	NS
BFP	36.0 (1.0)	29.4 (0.6)	< 0.001	27.2 (1.7)	21.9 (0.6)	0.002	39.3 (0.9)	35.6 (0.7)	0.007
Trunk fat %	53.6 (0.7)	55.8 (0.4)	0.01	59.3 (1.2)	60.7 (0.5)	0.01	51.5 (0.7)	51.6 (0.4)	NS
Appen-dicular fat %	43.1 (0.7)	40.9 (0.4)	0.01	37.0 (1.1)	35.9 (0.4)	NS	45.4 (0.7)	45.2 (0.4)	NS
ALM (kg)	19.0 (0.4)	22.9 (0.3)	< 0.001	23.7 (0.6)	28.5 (0.3)	< 0.001	17.2 (0.3)	18.1 (0.2)	0.01
ALM/h^2	6.8 (0.1)	7.7 (0.1)	< 0.001	7.7 (0.2)	8.8 (0.1)	< 0.001	6.4 (0.1)	6.7 (0.1)	0.03

Values are the mean, ± S.E. Statistically significant differences $p < 0.05$. BFP: Body Fat Percentage – fat % of total body mass); trunk fat % – percentage of trunk fat of total fat; appendicular fat % – percentage of appendicular fat of total fat; ALM –Appendicular Lean Mass; ALM/h^2 – ALM /height^2), NS – non-significant

Note: Adapted from Müller R et al. Factors Associated With Low Lean Mass in Early Rheumatoid Arthritis: A Cross-Sectional Study. Medicina (Kaunas). 2019 Nov 8;55(11) (licensed under Creative Commons)

When adjusted for age and gender, ERA patients had higher mean BFP, lower ALM values and higher odds of having unhealthy BC. 41.8% of the ERA patients and 19.8% of the controls had low lean mass (Table 8). 68.1% of the ERA subjects and 47.3% of the controls had a high body fat percentage and were classified as overfat. The adjusted odds of having the least favorable BC profile – sarcopenic overfat – were 4.4 times higher among the ERA group. The control subjects had 2.9 times higher odds of being neither sarcopenic nor overfat and being classified as having healthy BC than age- and gender-adjusted patients with ERA.

Table 8. Prevalence and age, gender adjusted odds for body composition phenotypes.

	Early RA N = 91		**Control group N = 328**			**aOR**	
	N (%)	**95% CI**	**N (%)**	**95% CI**	***p***	**(95% CI)**	***p***
Healthy BC	15 (16.5)	10.0, 25.1	130 (39.6)	34.5, 45.0	< 0.001	0.4 (0.2, 0.7)	0.01
Low lean mass	38 (41.8)	32.0, 52.0	65 (19.8)	15.8, 24.4	< 0.001	3.3 (1.9, 5.5)	< 0.001
Overfat	62 (68.1)	58.1, 77.0	155 (47.3)	41.9, 52.7	< 0.001	1.9 (1.1, 3.3)	0.02
Low lean mass+ overfat	24 (26.4)	18.2, 36.1	23 (7.0)	4.6, 10.2	< 0.001	4.4 (2.3, 8.4)	< 0.001

Age, gender adjusted odds ratio (aOR) for early RA group (binary logistic regression) healthy BC – normal lean mass, normal fat mass; low lean mass – low appendicular lean mass; overfat – high body fat percentage.
Note: Adapted from Müller R et al. Factors Associated With Low Lean Mass in Early Rheumatoid Arthritis: A Cross-Sectional Study. Medicina (Kaunas). 2019 Nov 8;55(11) (licensed under Creative Commons)

Factors associated with altered BC (Paper III)

Patients with ERA consumed less total food kilocalories per day (1534± 69) compared to the controls (1841±44; $p = 0.001$). Both men and women with ERA had lower daily protein intake, ERA patients consumed in average 23g less protein in a day compared to population controls ($p < 0.001$). Women with ERA consumed also less fat (the difference in males did not reach statistical significance), resulting in the mean daily fat intake in the ERA group 16 g lower compared to the control group ($p = 0.001$).

28% of men with ERA reached sufficient physical activity level recommended by the WHO compared to 64.2% of the control group ($p = 0.01$). However, over half (53%) of the women with ERA were sufficiently physically active, as were only 40.7% of the women in the control group ($p = 0.01$).

The factors associated with low lean mass differed between the groups (Table 9). Higher odds of having low lean mass in the ERA group were associated with higher inflammatory activity – ESR and CRP value, lower protein intake, corticosteroid usage, and lower quality of life (higher HAQ-DI score) after adjustment to age and gender.

In the control group, the low ALM was associated with age, insufficient physical activity, and smoking.

Table 9. Factors associated with low lean mass in the early RA and control group adjusted for age and gender.

	Early RA			Control group		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***
Age (years)*	1.00	0.98, 1.03	0.77	0.98	0.96, 0.99	0.006
Gender (male) *	2.23	0.87, 5.68	0.09	1.01	0.59, 1.75	0.96
ESR (mm/h)	1.026	1.002, 1.051	0.03	ND		
CRP (mg/l)	1.032	1.002, 1.063	0.04	0.99	0.91, 1.07	0.74
HAQ score (units)	2.41	1.24, 4.65	0.009	ND		
25 (OH) vitamin D (nmol/l)	1.00	0.98, 1.02	0.84	0.99	0.98, 1.01	0.30
Tender joint count (N/44)	1.02	0.97, 1.08	0.39	ND		
Swollen joint count (N/44)	1.03	0.95, 1.12	0.53	ND		
DAS 28 score (units)	1.22	0.91, 1.63	0.18	ND		
RF positive	1.10	0.42, 2.88	0.84	ND		
ACPA positive	1.20	0.46, 3.13	0.71	ND		
Current GCS user	3.71	1.39, 9.94	0.009	ND		
Current DMARD user	1.29	0.54, 3.09	0.57	ND		
Time from first symptoms	1.00	1.00, 1.00	0.55	ND		
Insufficient physical activity	0.51	1.00, 1.34	0.17	2.99	1.64, 5.46	<0.001
Smoking (ever)	1.40	0.53, 3.67	0.50	2.35	1.27, 4.33	0.006
Protein intake (g/day)	0.98	0.96, 0.99	0.04	1.00	0.99, 1.00	0.43

aOR: age, gender adjusted odds ratio (binary logistic regression) *: Unadjusted; HAQ score – Health Assessment Questionnaire; DAS 28 – Disease Assessment Score 28; RF – Rheumatoid Factor; ACPA – Anti-cyclic Citrullinated Peptide Antibodies; GCS – glucocorticosteroid; DMARD – Disease-Modifying Anti-Rheumatic Drug; sufficient physical activity – > 150 min moderate/75 min vigorous activity/week; ND – not done.

Note: Adapted from Müller R et al. Factors Associated With Low Lean Mass in Early Rheumatoid Arthritis: A Cross-Sectional Study. Medicina (Kaunas). 2019 Nov 8;55(11) (licensed under Creative Commons)

9. DISCUSSION

9.1. Cardiometabolic risk profile in early RA

9.1.1. Metabolic syndrome in early RA

The first aim of our study was to evaluate the cardiometabolic risk profile of subjects with early RA. The results of the study (paper I) indicate that metabolic co-morbidities of RA develop in the initial stage of the disease and are associated with altered body composition.

MetS is an important CVD risk factor linked to increased weight in the general population and in established RA, MetS has been found to be associated with subclinical atherosclerosis as well (Burggraaf et al., 2018).The prevalence of MetS in our early RA group was similar to what has been found previously in established disease (Zhang et al., 2013). We did not find a difference in the rate of MetS between RA (35.2%) and age/gender matched subjects in the control group (34.1%). There seems to be a significant heterogeneity in the presence of MetS in the general population, depending on the geographical region or population studied (Saklayen, 2018). It is reasonable to believe that the same applies to MetS in RA as well. To our knowledge, this is the first study evaluating MetS in a European early RA group.

Presence of metabolic syndrome according to body weight

Confirming the association between obesity and MetS, the prevalence of MetS and its components was significantly higher in overweight/obese subjects in both of our study groups. A new finding was that the odds of having MetS were 5.6 times higher among the RA group with normal weight- a phenomenon called normal weight metabolic obesity, while MetS was rare in controls in the same weight group. There is no standard definition for normal weight metabolically unhealthy/obese phenotype where a lean person carries multiple cardiometabolic risk factors traditionally associated with obesity (Ding et al., 2016). In previous studies, the rate of normal weight metabolic obesity in general population has ranged from 5% to 45% (Ding et al., 2016; N. Eckel et al., 2015; Mathew et al., 2016). This phenomenon has not been previously described in early RA. Data on the long-term outcomes of this unhealthy phenotype is limited, but it has been associated with increased markers of atherosclerosis, higher prevalence of non-alcoholic fatty liver disease, subclinical systolic, diastolic dysfunction and angiographic coronary artery disease (Mathew et al., 2016).

The presence of metabolic obesity in early RA patients with normal weight may contribute to the “obesity paradox” in RA, a higher CVD risk in patients with normal weight (Baker et al., 2015; England, Baker, et al., 2018) associated with a change in BC and an excess of metabolically active fat tissue in RA patients with normal BMI, as reported in previous studies (Book et al., 2009; Giles et al.,

2010). The pathophysiological background and long-term consequences of the normal-weight metabolically obese phenotype present in the early stage of RA should be established in future studies.

Components of metabolic syndrome

An important finding in early RA group reported in paper I was a high prevalence of **hypertension** – one of the strongest predictors of cardiovascular disease. Hypertension was found in a higher proportion of early RA patients (73%) compared to controls (61%). In previous studies, the reported prevalence of hypertension in RA has been widely variable, ranging from 4% to 73% (Boyer et al., 2011; Nurmohamed et al., 2015). In our study the difference between RA patients and control group was especially substantial in the normal BMI subgroup, in which early RA patients had 2.8 times higher odds of having hypertension compared to age/gender matched controls. This result differs from the findings of an earlier study that associated hypertension in RA mainly with obesity (Morović-Vergles et al., 2013). Even more concerning was the fact that the proportion of patients with elevated blood pressure but without antihypertensive treatment was significantly higher among RA patients. Only 31% of RA patients with elevated blood pressure received treatment, compared to 53% of controls with hypertension. This is in line with reports of several previous groups describing low prevalence of treated hypertension in RA (proportion of patients with hypertension and receiving treatment ranging from 22% to 34%) (Panoulas et al., 2008). Blood pressure can be increased in RA due to the effect of chronic inflammation, altered body composition, insulin resistance, and increased peripheral resistance due to atherosclerosis, but also due to NSAID use and low physical activity (Panoulas et al., 2008). Which of these factors is the main underlying mechanism leading to hypertension in early arthritis needs further in-depth analysis in larger cohorts. Hypertension is a condition of established importance in the development of CVD that can be easily and noninvasively diagnosed and treated. Blood pressure monitoring should be a routine procedure in the follow-up of all patients with RA from the initial stage of the disease, as now recommended by EULAR (Agca et al., 2017).

Previous studies have shown an association between RA, **hyperglycemia** and diabetes. The odds of diabetes in RA have been reported to be 1.74 times higher compared to the general population and the difference is believed to be induced mainly by the presence of IR (Boyer et al., 2011; Nicolau et al., 2017). Diabetes is a recognized independent risk factor for CVD in RA as well as in the general population (Chung et al., 2008; Patel et al., 2016). In our study, there was no difference between the rates of hyperglycemia, diabetes or obesity in the early RA and control subjects. Looking into the normal-weight subgroup, patients with early RA had a significantly higher prevalence of hyperglycemia compared to controls, pointing to the role of altered body composition and the possible role played by hidden IR (Chung et al., 2008; Zhang et al., 2013).

9.1.2. Insulin resistance in early RA

In paper II of this study, we aimed to fill the gap in knowledge around evaluating the presence of IR in early RA. The prevalence of IR is rising worldwide due to obesity epidemics as the decrease in the general population's insulin sensitivity is primarily associated with increased weight (Abbasi et al., 2002; Martinez et al., 2017). The association between established RA and IR is well known (Nicolau et al., 2017), but only a few studies have looked into this in the early stage of the disease, with inconclusive results (AbouAssi et al., 2014; Manrique-Arija et al., 2015; Mirjafari et al., 2011; Shahin et al., 2010). In our group, early RA patients had 4.8 times higher odds of having IR compared to the general population (adjusted to age and gender). Due to methodological differences (criteria for RA and IR, and cut-off points) studies conducted to evaluate the prevalence of IR in ERA are hard to compare. Frequently observed IR in the initial stage of RA is of high importance, as IR in the general population is considered to be one of the most important contributors to CVD. In RA, the topic is a bit more controversial. Some groups have confirmed the associated risk, and others have denied an association between the presence of IR in RA and elevated CV risk (Chung et al., 2008; Giles et al., 2015; González-Gay et al., 2015; Guin et al., 2019; Montagna et al., 2007), but data from long-term observational studies is currently not available.

9.1.3. Factors associated with IR in early RA

Differences between the groups were the most remarkable among male ERA patients and controls (men with ERA had 7.4 times higher odds of being classified as insulin resistant than women of the same group). The association between male gender and IR has been noted in the general population but gender differences in the presence of IR in RA have not been described before. The difference in BC with elevated visceral adipose tissue compared to women, lower adiponectin levels, and inflammation induced decrease in androgen levels, are believed to be the main contributing factors to the higher prevalence of IR among men (Geer & Shen, 2009; Rao et al., 2013) and could be the factors contributing to the difference between men and women, to an even higher extent in RA.

Additionally, looking into the associations between BC and IR, we found that lower appendicular lean mass was indeed associated with IR in the ERA group, but not in the control group. Several previous studies have shown the relationship between adipose tissue and IR in ERA, and adipose tissue is thought to be the main factor responsible for IR in the general population (AbouAssi et al., 2014; Martinez et al., 2017; Mirjafari et al., 2011). To our knowledge, this is the first study showing an increased likelihood of IR in ERA associated with lower muscle mass. The role of skeletal muscle loss in the development of IR has been shown in the general population (Srikanthan et al., 2010; Srikanthan & Karlamangla, 2011). The concept of BC change, loss of lean mass, and gain in fat tissue in RA is well established (Challal et al., 2015; Santo et al., 2018). Muscle mass is an

important determinant of glucose and energy homeostasis (Cleasby et al., 2016). The relationship of IR and sarcopenia has been described as a self-contained loop where loss of muscle is associated with intramuscular fat infiltration and enhanced production of inflammatory cytokines, as well as lipotoxicity, mitochondrial dysfunction, oxidative stress, and anabolic resistance leading to IR. In turn, these disturbances exacerbate sarcopenia (Cleasby et al., 2016; Tournadre et al., 2017, 2018).

The results of our study concerning disease-specific measures and IR were quite expected and similar to what has been found before. IR in RA has been associated with unfavorable prognostic markers – disease activity, seropositivity, and higher inflammatory activity (Nicolau et al., 2017). We found that IR was associated with higher levels of inflammatory markers (CRP, TNF-alpha, and IL-6), and higher disease activity, but did not see an association with seropositivity. In a multivariate model, high disease activity (DAS28 score) remained statistically significant, confirming the association between high inflammatory burden and IR. High disease activity in the early stage of the disease is associated with worse prognosis, and our findings suggest that IR is tightly connected to adverse RA outcomes, and could be the reason behind a rise in cardiovascular mortality in the early stage, with elevated risk in patients with a higher inflammatory burden (Gonzalez et al., 2008; Goodson et al., 2004; Humphreys et al., 2014).

9.1.4. Body composition in early RA

The third paper focused on the differences in BC between early RA and control subjects, concentrating on factors associated with changes in lean mass. To our knowledge, this is the first study that has assessed both the role of lifestyle (diet and physical activity) and disease specific parameters in association with low lean mass in ERA.

The majority of patients with established RA are affected by BC alteration – lean mass loss and fat mass gain (Rall & Roubenoff, 2004; Summers et al., 2010) – but only a couple of studies have looked into this phenomenon in early RA (Book et al., 2009; Dao et al., 2011; Turk et al., 2018). We found that the BC of patients with recent onset RA differs from control subjects- ERA patients have lower appendicular lean mass, higher body fat percentage, and a higher prevalence of unhealthy BC phenotypes. 42% of subjects in the ERA group were classified as having low lean mass, 68% had a high body fat percentage, and 26% had the least favorable BC phenotype: a combination of low lean mass and overfat. Only 16% of patients with ERA had no unhealthy BC components. Our results confirm that the change in BC in RA develops early in the course of the disease (Book et al., 2009; Dao et al., 2011; Turk et al., 2018). The mean ALM values reported by a Swedish ERA study were quite similar to the ones found by us –17.2 kg in women and 22.5 kg in men, compared to 17.2 kg and 23.7 kg respectively in our study) (Book et al., 2009). Population-specific differences in BC parameters make direct comparisons with other groups difficult. For example, people originating from

Asia tend to have a higher fat mass and lower lean mass in relation to BMI compared to people of European origin. In a study evaluating BC in Vietnamese women with ERA, the mean ALM was 12.9 kg (Dao et al., 2011). In a recent early arthritis study in the Netherlands, a 5–7% lower ALM was found in DMARD naïve early arthritis patients compared to age matched controls, but only data from subjects over the age of 50 was analyzed (Turk et al., 2018). These results hint that the obesity paradox – elevated CVD risk in normal weight patients – can already be mediated by alteration in BC in the disease's early stage. To confirm the hypothesis, long-term observational studies looking into markers of subclinical atherosclerosis and CVD mortality are needed.

9.1.5. Factors associated with BC in early RA

In our study, the presence of low lean mass was not associated with the duration of symptoms of arthritis, suggesting that disease-specific pre-clinical factors are the main contributors to the change. A Swedish study (Book et al., 2009) found an association between disease duration and lower lean mass in females in its initial evaluation, but a follow-up after two years (Book et al., 2011) came to the conclusion that age-related loss of lean mass and gain in fat mass are less expressed in RA compared to controls. A group in the Netherlands controversially found that a longer symptom duration was associated with a higher lean (and fat) mass, but only in male subjects (Turk et al., 2018).

In light of the knowledge that BC change in RA leads to a cascade of metabolic abnormalities, including insulin resistance and metabolic syndrome, enhancing endothelial dysfunction and leading to elevated cardiovascular risk (Challal et al., 2015; Delgado-Frías et al., 2015; Elkan et al., 2009), the findings in the initial stage of the disease emphasize the need to find an efficient intervention to prevent changes in BC.

Inflammation induced catabolism is considered to be responsible for the development of the loss of lean tissue and fat accumulation characteristic to established RA (Engvall et al., 2008; Rall & Roubenoff, 2004; Summers et al., 2010). Sarcopenia is a recognized comorbidity in several other chronic inflammatory conditions, low-grade chronic inflammation is associated with biologic aging, and higher levels of CRP and IL-6 are considered to be predictors of age-related sarcopenia (Kalyani et al., 2014; Wilson et al., 2017). We found that decreased lean mass was associated with an acute phase response (ESR, CRP). No association was found between the presence of low lean mass and prognostic factors (ACPA/RF positivity) or indices (DAS28, joint counts) that correlate with disease burden and the reduction of physical activity as a consequence. The finding suggests that BC could be improved by controlling inflammation. Of previous ERA studies, one found a weak association between low lean mass and disease activity (Book et al., 2009), but this finding was not replicated by other researchers (Dao et al., 2011; Turk et al., 2018). However, results regarding the effects of DMARD treatment on BC have been mixed. BC can be stabilized by achieving remission via tightly

controlled therapy, (Book et al., 2009), but the lean mass loss cannot be reversed, even with early treatment (Lemmey et al., 2016; S. M. Marcora et al., 2006). The only medication that has shown an ability to alter BC is an IL-6 inhibitor – an increase in lean mass was observed after one year of treatment with tocilizumab, possibly through the regulation of leptin that conventional DMARDs and anti-TNF agents are not capable of mediating (Tournadre et al., 2017). An additional possible explanation for the lack of treatment effects is that the change in BC occurs very early in the course of RA, probably in the preclinical phase, and is resistant to alteration without specific pro-anabolic interventions (Lemmey et al., 2016).

While DMARD treatment can potentially stabilize BC alteration, the long-term effects of GCS, another commonly used medication in RA, which leads to muscle wasting, fat accumulation, and fat redistribution, is a well-known phenomenon (Buttgereit & Burmester, 2016; Cutolo et al., 2014). We found short-term GCS usage (mean dose of prednisolone 13.8 mg, mean time from diagnosis 37 days) to be associated with 3.7 *times* higher odds of having low lean mass among the ERA subjects. The duration of DMARD therapy was too short to have a direct effect on BC. The limited data on the short-term effects of GCS use on BC parameters shows mixed results. Glucocorticoid therapy can have a double-edged impact on muscle mass – a positive effect resulting from the rapid reduction of inflammation, and a negative one by inducing protein breakdown and decreasing synthesis (Buttgereit & Burmester, 2016). Looking into previously published data, Dao et al. did not find GCS usage to be associated with a change in BC in early RA (Dao et al., 2011). The results of the COBRA study (a comparison of intense remission aiming treatment strategies in ERA) show an increase in FM without lean mass reduction in patients treated with high-dose, step-down GCS regimens after 26 weeks (Konijn et al., 2016), indicating that a rapid decrease in inflammation counteracted the negative effects on BC. Inversely, a loss of lean mass was recently reported after a single high-dose intramuscular GCS injection (Lemmey et al., 2018).

Data reported in ageing-related sarcopenia show that in addition to chronic inflammation, reduced physical activity and an inadequate diet are important contributors to the loss of lean mass (Beaudart et al., 2017; Cruz-Jentoft et al., 2019; Dent et al., 2018; Wilson et al., 2017). Protein supplementation is one of the options suggested for the treatment of sarcopenia (Beaudart et al., 2017; Dent et al., 2018; Geirsdottir et al., 2013). In the only study we found where the role of nutrition in RA induced muscle loss was assessed, no association was found between protein intake and sarcopenia in established RA (Barone et al., 2018). It has been suggested that diet and protein intake in patients with RA is not different from healthy controls (Challal et al., 2015; Rall & Roubenoff, 2004; Roubenoff, 2009). Evaluating food intake using the 24-hour dietary recall, we found that early RA patients consumed fewer total calories and had lower fat and protein intake than control subjects. Low protein intake was associated with the presence of low lean mass (adjusted to age and gender). The 24HDR method provides detailed intake data but cannot account for day-to-day variability and is unable to assess long-term dietary exposure. There is no comparable data on the role of

nutrition in preventing of BC alterations, in RA but there is some evidence that dietary change may provide benefits in reducing disease activity (Chehade et al., 2019; Cutolo & Nikiphorou, 2018; Petersson et al., 2018). The difference in nutrient intake between early RA and control subjects suggests that nutritional advice may have a valuable role in RA patient education, especially important to the patients with highest risk of lean mass loss – those on current glucocorticoid therapy. Further studies need to be performed to validate the potential benefits of nutrition and protein supplementation to prevent the loss of lean mass in RA.

Sedentary lifestyle and immobility are established risk factors for sarcopenia in the elderly, and maintaining sufficient physical activity is the cornerstone for preventing of age-related muscle loss (Beaudart et al., 2017; Dent et al., 2018). It is well known that the majority of RA patients are physically inactive due to the movement limitations induced by arthralgia, stiffness, and active inflammation (Rall & Roubenoff, 2004; Sokka T. et al., 2008). High intensity resistance training has been shown to improve BC in RA, but is difficult to implement long-term due to low adherence (Lemmey et al., 2009; Morsley et al., 2018; Rall & Roubenoff, 2004). Looking into previously published data, a lower frequency of regular intentional exercise has been observed in female sarcopenic early RA subjects in Vietnam (Dao et al., 2011). We found a notable gender difference in physical activity – women with ERA were more active than female controls, but the opposite was found in men, mirroring the higher disease activity observed in male subjects. After age and gender were adjusted for, we found the low ALM to be associated with low physical activity level among control subjects, but we did not find an association between physical activity and low lean mass in the ERA group. This finding, in light of the association between elevated inflammatory markers and low lean mass, emphasizes that hypermetabolism caused by inflammation (Rall & Roubenoff, 2004) is more important in the loss of muscle tissue in RA than low physical activity: the main determinant of low lean mass among the general population.

Finally, in accordance with results from previous studies in early and established RA (Book et al., 2009; Dao et al., 2011; Giles, Bartlett, et al., 2008; Giles, Ling, et al., 2008), we confirmed an association between low lean mass and disability – a 2.4 *times* increase in the odds of low lean mass was observed per every unit increase in the HAQ-DI score.

9.2. Limitations

Several limitations to our study should be acknowledged and taken into account when interpreting the findings. The modest sample size of the ERA group limited possibilities in statistical analysis. The difference in age and gender composition between RA subjects and population-based comparison group for papers II and III did not allow direct comparison between the groups, although age and gender adjustments were used in data analysis to limit bias.

The patients enrolled in our study were not treatment-naïve – 55% were on DMARD treatment and 29% received corticosteroids. The lack of pre-treatment data can also be considered a limitation. It is unlikely this had an impact on the BC measures or presence of cardiometabolic risk factors, but it may have interfered with the disease activity and inflammatory status assessment.

The fact that there are no validated criteria for sarcopenia in RA complicates comparisons with previous reports. The current EWGSOP criteria are designed to be used with an elderly population (Cruz-Jentoft et al., 2019) and may underestimate the presence of sarcopenia in the general population and overestimate it in RA.

10. CONCLUSIONS

1. Patients with early RA have an increased risk of metabolic obesity – a phenomenon where metabolic syndrome develops at a normal weight status.
2. Subjects with early RA have higher blood pressure than controls, but the proportion of rheumatoid patients receiving antihypertensive medication is lower, showing an underestimated need for treatment in this group.
3. An important contributor to cardiovascular morbidity – insulin resistance is already present in a majority of RA patients in the early stage of the disease. Male gender and high inflammatory activity increase the risk of insulin resistance.
4. The presence of insulin resistance cannot be predicted by body weight in RA, as reduced insulin sensitivity is associated with low lean mass.
5. A change in body composition can be detected in the first months after the onset of synovitis in RA. Patients with early RA have a lower appendicular lean mass adjusted to body size and a higher body fat percentage compared to healthy controls.
6. The presence of low lean mass in early RA is associated with higher inflammatory activity, glucocorticoid treatment, and lower protein intake, but not with age, physical activity, or smoking, as seen in control subjects.

The findings of this study help to clarify the alterations in cardiometabolic risk profile in early RA. The results are important, as due to the potential of unrecognized CVD in RA, a proactive approach in screening from the earliest phase of the disease is crucial for timely and appropriate intervention.

11. SUMMARY IN ESTONIAN

Kardiometaboolsed riskitegurid ja keha koostise muutused varase reumatoidartriidi haigetel

SISSEJUHATUS

Reumatoidartriit (RA) on kõige sagedasem krooniline süsteemne põletikuline haigus levimusega 0,5–2%. RA korral kujuneb liigeskahjustus koos liigeseväliste nähtudega ja seejuures võib iseloomulik autoimmuunprotsess alata enne artriidi kliinilist avaldumist.

Viimastel aastatel on RA ravis toimunud kiire areng, mis on suunatud võimalikult varasele põletiku pärssimisele (Smolen & Aletaha, 2015), kuid vaatamata sellele ei ole RA patsientide elumus paranenud (Giles, 2019). RA-ga seonduv kõrgem suremus on tingitud peamiselt kardiovaskulaarsüsteemi haigustest, kuid lisarisk ei ole täielikult seletatav traditsiooniliste riskitegurite nagu rasvumine, diabeet, hüperkolesteroleemia jt esinemisega (Agca et al., 2017; Cutolo et al., 2014; Giles, 2019). Südame-veresoonkonna haiguste esinemissageduse tõusu on kirjeldatud juba artriidi kliinilise avaldumise järel (Błyszczuk & Szekanecz, 2020; England, Thiele, et al., 2018) ja aterogeense protsessi algus on võimalik juba prekliinilises staadiumis (Bartoloni et al., 2010).

Rasvumine on üldrahvastikus üks olulisemaid südame-veresoonkonna haiguste riski tõstvaid tegureid. RA korral seostub rasvumine leebema haiguse kuluga ning väljakujunenud RA-ga rasvunud patsientidel on pigem madalam südame-veresoonkonna haiguste ja suremuse risk võrreldes normkaalulistega (England, Thiele, et al., 2018; George & Baker, 2016).

Rasvumisega seotud kardiometaboolsete riskitegurite kogumit nimetatakse metaboolseks sündroomiks. Metaboolse sündroomi komponendid seonduvad koos esinedes kõrgema riskiga kardiovaskulaarhaiguse tekkeks kui igaüks neist eraldiseisvalt (R. H. Eckel et al., 2005). Kui üldrahvastikus on metaboolse sündroomi esinemine seotud peamiselt adipoossusega, siis RA korral ei ole metaboolsete riskitegurite esinemine kehakaalust sõltuv (Kerekes et al., 2014). Varasemad uuringud RA korral on näidanud, et väljakujunenud haigusega patsientidel on kõrgem metaboolse sündroomi esinemissagedus, kuid on ebaselge, millal need muutused kujunevad.

Metaboolse sündroomiga seostub insuliinresistentsus (IR): insuliini ebapiisav toime glükoosi ainevahetuse regulatsioonis vähenenud vastuse tõttu perifeersetes kudedes. IR ei ole ainult glükoosi metabolismi häire, vaid ka oluline iseseisev ateroskleroosi ja kardiovaskulaarhaiguse teket mõjutav tegur (Laakso, 2015). RA korral on IR esinemissagedus oluliselt kõrgem kui üldrahvastikus, seostudes enam kõrgema põletikulise aktiivsuse ja haiguse raskuse kui kehakaaluga (Nicolau et al., 2017).

Lihasmassi, lihasjõu ja funktsionaalse võimekuse langus sarkopeenia on tüüpiline vananemisega kaasnev seisund. Samalaadseid muutusi kirjeldatakse ka

mitmete krooniliste haiguste sh reumatoidartriidi korral. Vananemisega seotud lihaskao põhjuseks peetakse muutusi toitumises, vähenenud kehalist aktiivsust ja kroonilist madala aktiivsusega põletikku (Beaudart et al., 2017; Cruz-Jentoft et al., 2010). Sarkopeenia tagajärjeks on elukvaliteedi langus, kukkumised, osteoporoos, düslipideemia ja metaboolne sündroom, mis omakorda suurendavad südame-veresoonkonna haiguste riski ja suremust (Cruz-Jentoft et al., 2010; Marzetti et al., 2017).

Kui lihasmassi vähesusele kaasneb liigne rasvkude, nimetatakse seda sarkopeeniliseks rasvumiseks: rasv ladestub vistseraalselt ja infiltreerib skeletilihaseid. Selline seisund seostub sügavama insuliinitundlikkuse häire, madalama funktsionaalse võimekuse, elukvaliteedi ja elumusega kui rasvumine ja sarkopeenia eraldi (Cruz-Jentoft et al., 2019).

Väljakujunenud haigusega RA patsientidest on sarkopeenilist rasvumist ilma kehamassi muutuseta kirjeldatud kuni 2/3 juhtudest (Challal et al., 2015; Summers et al., 2010) ja see võib olla üheks põhjuseks, miks normkaalulistel RA patsientidel on täheldatav kõrgem suremusrisk võrreldes rasvunutega (England, Thiele, et al., 2018).

Lihasmassi kadu RA korral on seotud sarkoaktiivsete põletikumediaatorite üleproduktsiooniga; oma roll võib olla ravimitel ja vähesel liikumisel (Tournadre et al., 2018). Keha koostise muutuse algus RA korral ei ole päris selge. Mõned autorid on avaldanud arvamust, et muutused kujunevad juba prekliinilises faasis (Giles, 2019). Uuringud Rootsis, Vietnamis ja Hollandis (Book et al., 2009; Dao et al., 2011; Turk et al., 2018) on kinnitanud, et varase artriidiga patsientidel on oluliselt madalam lihasmass võrreldes üldrahvastikuga. Andmed selle kohta, millised tegurid on muutuse tekkega seotud, on vastukäivad, peamiselt on hinnatud haigusega seotud tegurite (artriidi aktiivsus, ravi, prognostilised faktorid) mõju ilma, et oleks arvestatud eluviisi rolli.

UURINGU EESMÄRGID

Üldiseks eesmärgiks oli hinnata kardiometaboolset riski mõjutavaid tegureid varase RA korral. Töö oli suunatud keha koostise muutuste hindamisele ning seostele metaboolsete faktoritega varase RA patsientidel võrreldes üldrahvastikuga.

Töö eesmärgid:

1. Hinnata kardiometaboolse riski profiili varase RA korral metaboolse sündroomi, selle komponentide (artikkel I) ja insuliinresistentsuse (artikkel II) esinemise kaudu.
2. Selgitada insuliinresistentsuse kujunemisega seotud tegureid varase RA haigetel (artikkel II)
3. Võrrelda keha koostist varase RA korral ja tervetel inimestel (artikkel III)
4. Uurida seoseid keha koostise ning haigusega seotud tegurite, kehalise aktiivsuse ja toitumise vahel RA algfaasis (artikkel III)

UURITAVAD JA MEETODID

Uuritavad

Varase RA haigete grupis osales 92 järjestikust Tartu Ülikooli Kliinikumis reumatoloogi vastuvõtule pöördunud RA diagnoosiga patsienti, kelle puhul olid täidetud ACR/EULAR 2012. a reumatoidartriidi klassifikatsiooni kriteeriumid (Aletaha et al., 2010) ja vaevused ei olnud kestnud üle ühe aasta.

Artiklis I kasutasime võrdlusgrupina 273 vanusele (+/– 3a) ja soole sobitatud uuritavat suhtes 3 kontrolli 1 RA patsiendi kohta, kes olid juhuslikult valitud 2008–2009 a kolmes Eesti maakonnas läbi viidud rahvastikupõhises uuringus osalenute seast.

Rahvastikupõhisesse kontrollgruppi (artiklid II ja III) oli kaasatud juhuvalim perearsti nimistust (332 uuritavat), kelle vanuseline ja sooline jaotus vastas Eesti rahvastiku 2013. a hinnatud struktuurile.

Meetodid

RA gruppi kuuluvaid uuritavaid küsitleti esmaste haigusnähtude tekke kohta, hinnati kaasuvate haiguste olemasolu ja ravimite kasutamist. RA diagnoos kinnitati elektroonilise haigusloo andmete põhjal ja uuritavad klassifitseeriti ACR/EULAR 2012 kriteeriumide alusel.

Füüsilisel läbivaatusel fikseeriti RA patsientidel turses ja valulike liigeste arv, kõigil uuritavatel mõõdeti kehakaal, pikkus, vöö ümbermõõt ja vererõhk. Artriidi aktiivsus määratleti DAS28 skoori abil.

RA patsientide elukvaliteeti hinnati tervisehinnangu küsimustiku (HAQ-DI) alusel. Kehalise aktiivsuse tase määratleti vastavalt WHO soovitustele kasutatdes rahvusvahelise füüsilise aktiivsuse küsimustiku (IPAQ) andmeid.

Patsienti küsitleti viimase ööpäeva jooksul tarvitud toidu ja joogi kohta 24 tunni toiduintervjuu meetodil. Andmed sisestati Tervise Arengu Instituudi poolt välja töötatud NutriData programmi, hinnati energiasisaldust ja toitainete kogust tarbitud toidus.

Paastuplasmas määrati veresuhkru, ESR, CRV, kolesterooli, HDL ja triglütseriidide väärtused ning RA autoantikehade (RF ja antiCCP) olemasolu. Vereseerumis mõõdeti IL-6, TNF-alfa ja insuliini tase.

Metaboolne sündroom defineeriti NCEP ATP III kriteeriumide alusel, normkaalulised metaboolse sündroomiga patsiendid klassifitseeriti metaboolselt rasvunutena. Rahvastikupõhise kontrollgrupi homeostaasimudeli (HOMA-IR) ülemise kvartiili alusel määrati insuliinresistentsuse olemasolu.

Kehamassiindeksi alusel jagati uuritavad normkaalulisteks, ülekaalulisteks ja rasvunuteks. Kvantitatiivseks lihas- ja rasvkoe massi hindamiseks kasutati DEXA meetodil saadud tulemusi ja arvutuslikke indekseid. Lihasmassi hinnati jäsemete lihaskoe massi põhjal, rasvkoe massi keha kogu rasvamassi ja rasvaprotsendi alusel, piirväärtused määrati kontrollgrupi andmete põhjal.

TULEMUSED JA JÄRELDUSED

1. Varase reumatoidartriidi haigete ning vanusele ja soole vastava kontrollgrupi vahel ei olnud erinevust kehamassi indeksis ega metaboolse sündroomi esinemises (35,2% RA *vs* 34,1% kontrollgrupis). Reumatoidartriidiga patsientidel esines 5,6 korda enam metaboolset rasvumist – seisundit, kus metaboolne sündroom kujuneb normkaalu juures. Metaboolne sündroom esines 16,7% normkaalulistest varase RA grupis ja 2,3% kontrollgrupi samas kaalurühmas.
2. Varase RA-ga patsientidel olid kõrgemad nii süstoolse kui ka diastoolse vererõhu väärtused. Hüpertensioon esines 72,5% RA patsientidest ja 61% kontrollrühmas. Alahinnatud ravivajadust RA patsientidel näitas oluliselt väiksem kõrgvererõhktõve ravi saavate RA patsientide osakaal (31%) võrreldes kontrollgrupiga (53%).
3. Insuliinresistentsus kui oluline kardiovaskulaarriskiga seonduv tegur esines suuremal osal RA patsientidest juba varases haiguse staadiumis. Keskmine insuliini tase oli RA korral oluliselt kõrgem kui kontrollgrupis. IR tõenäosus varase RA patsientidel oli 4,8 korda kõrgem kui kontrollgrupis.
4. Leidsime, et RA korral kehakaal ei ennusta insuliinresistentsuse olemasolu. RA grupis oli insuliinresistentsuse võimalus 7,4 korda kõrgem meessoost patsientidel võrreldes naistega; 6,2 korda kõrgem haiguse aktiivsuse korral võrreldes madala haiguse aktiivsusega patsientidega ja insuliinresistentsuse tõenäosus suurenes lihasmassi vähenedes.
5. Keha koostise muutus oli täheldatav juba RA kliinilise avaldumise esimestel kuudel. Varase RA patsientidel oli madalam jäsemete lihasmass keha pindala kohta ja kõrgem rasvkoe osakaal võrreldes kontrollgrupiga. Lihasmass oli madal 42% varase RA patsientidest (kontrollgrupis 20%) ja kõrge rasvkoe hulk 68% patsientidest (47% kontrollidest). Igal neljandal varase RA haigel (26%) leiti samaaegselt nii madal lihasmass kui ka liigne rasvkude (7% kontrollgrupis). Vanusele ja soole kohandades oli varasesse RA gruppi kuuluvatel patsientidel 3,3 korda kõrgem võimalus madala lihasmassi esinemiseks, 1,9 korda kõrgem võimalus liigse rasvkoe esinemiseks ja 4,4 korda kõrgem tõenäosus samaaegseks liigse rasvkoe ja madala lihasmassi esinemiseks.
6. Leidsime, et madala lihasmassiga seotud tegurid varase RA patsientidel ja kontrollgupis olid erinevad. Suurema šansiga madala lihasmassi esinemiseks (kohandatuna vanusele ja soole) olid RA grupis seotud kõrgem põletikuline aktiivsus, madalam ööpäevane valgu tarbimine toiduga, glükokortikosteroidide kasutamine ja madalam elukvaliteet. Kontrollgrupis oli madala lihasmassi esinemine seotud kõrgema vanuse, madala füüsilise aktiivsuse ja suitsetamisega.

Uurimus näitas varase RA korral esinevaid kehakaaluga mitte seotud eripärasid kardiometaboolse riskiprofiilis. Metaboolsed häired nagu insuliinresistentsus, metaboolne sündroom, keha lihaskoe ja rasvkomponendi muutused normaalse kehakaalu juures on iseloomulikud alates haiguse algusest. Tulemused on olulised RA haigete südame-veresoonkonna kahjustuse riskiprofiili hindamisel ja mõjutamisel adekvaatse ja õigeaegse raviga.

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13. REFERENCES

Abbasi, F., Brown, B. W., Lamendola, C., McLaughlin, T., & Reaven, G. M. (2002). Relationship between obesity, insulin resistance, and coronary heart disease risk. *Journal of the American College of Cardiology*, *40*(5), 937–943. https://doi.org/10.1016/S0735-1097(02)02051-X

Abhishek, A., Nakafero, G., Kuo, C.-F., Mallen, C., Zhang, W., Grainge, M. J., & Doherty, M. (2018). Rheumatoid arthritis and excess mortality: Down but not out. A primary care cohort study using data from Clinical Practice Research Datalink. *Rheumatology (Oxford, England)*, *57*(6), 977–981. https://doi.org/10.1093/rheumatology/key013

AbouAssi, H., Tune, K. N., Gilmore, B., Bateman, L. A., McDaniel, G., Muehlbauer, M., Huebner, J. L., Hoenig, H. M., Kraus, V. B., St Clair, E. W., Kraus, W. E., & Huffman, K. M. (2014). Adipose depots, not disease-related factors, account for skeletal muscle insulin sensitivity in established and treated rheumatoid arthritis. *The Journal of Rheumatology*, *41*(10), 1974–1979. https://doi.org/10.3899/jrheum.140224

Abourazzak, F. E., Mansouri, S., Najdi, A., Tahiri, L., Nejjari, C., & Harzy, T. (2014). Prevalence of metabolic syndrome in patients with rheumatoid arthritis in Morocco: A cross-sectional study of 179 cases. *Clinical Rheumatology*, *33*(11), 1549–1555. https://doi.org/10.1007/s10067-014-2570-x

Agca, R., Heslinga, S. C., Rollefstad, S., Heslinga, M., McInnes, I. B., Peters, M. J. L., Kvien, T. K., Dougados, M., Radner, H., Atzeni, F., Primdahl, J., Södergren, A., Jonsson, S. W., Rompay, J. van, Zabalan, C., Pedersen, T. R., Jacobsson, L., Vlam, K. de, Gonzalez-Gay, M. A., … Nurmohamed, M. T. (2017). EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Annals of the Rheumatic Diseases*, *76*(1), 17–28. https://doi.org/10.1136/annrheumdis-2016-209775

Alberti, K. G., & Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Medicine: A Journal of the British Diabetic Association*, *15*(7), 539–553. https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S

Aletaha, D., Neogi, T., Silman, A. J., Funovits, J., Felson, D. T., Bingham, C. O., Birnbaum, N. S., Burmester, G. R., Bykerk, V. P., Cohen, M. D., Combe, B., Costenbader, K. H., Dougados, M., Emery, P., Ferraccioli, G., Hazes, J. M. W., Hobbs, K., Huizinga, T. W. J., Kavanaugh, A., … Hawker, G. (2010). 2010 rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Annals of the Rheumatic Diseases*, *69*(9), 1580–1588. https://doi.org/10.1136/ard.2010.138461

American Diabetes Association. (2014). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*, *37*(Supplement 1), S81–S90. https://doi.org/10.2337/dc14-S081

Anderson, J., Caplan, L., Yazdany, J., Robbins, M. L., Neogi, T., Michaud, K., Saag, K., O'Dell, J. R., & Kazi, S. (2012). Rheumatoid Arthritis Disease Activity Measures: American College of Rheumatology Recommendations for Use in Clinical Practice. *Arthritis Care & Research*, *64*(5), 640–647. https://doi.org/10.1002/acr.21649

Antonopoulos, A. S., & Tousoulis, D. (2017). The molecular mechanisms of obesity paradox. *Cardiovascular Research*, *113*(9), 1074–1086. https://doi.org/10.1093/cvr/cvx106

Arts, E. E. A., Popa, C., Broeder, A. A. D., Semb, A. G., Toms, T., Kitas, G. D., Riel, P. L. van, & Fransen, J. (2015). Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *74*(4), 668–674. https://doi.org/10.1136/annrheumdis-2013-204024

Avina-Zubieta, J. A., Thomas, J., Sadatsafavi, M., Lehman, A. J., & Lacaille, D. (2012). Risk of incident cardiovascular events in patients with rheumatoid arthritis: A meta-analysis of observational studies. *Annals of the Rheumatic Diseases*, *71*(9), 1524–1529. https://doi.org/10.1136/annrheumdis-2011-200726

Baker, J. F., Billig, E., Michaud, K., Ibrahim, S., Caplan, L., Cannon, G. W., Stokes, A., Majithia, V., & Mikuls, T. R. (2015). Weight Loss, the Obesity Paradox, and the Risk of Death in Rheumatoid Arthritis. *Arthritis & Rheumatology (Hoboken, N.J.)*, *67*(7), 1711–1717. https://doi.org/10.1002/art.39136

Baker, J. F., George, M., Baker, D. G., Toedter, G., Von Feldt, J. M., & Leonard, M. B. (2011). Associations between body mass, radiographic joint damage, adipokines and risk factors for bone loss in rheumatoid arthritis. *Rheumatology (Oxford, England)*, *50*(11), 2100–2107. https://doi.org/10.1093/rheumatology/ker294

Barone, M., Viggiani, M. T., Anelli, M. G., Fanizzi, R., Lorusso, O., Lopalco, G., Cantarini, L., Di Leo, A., Lapadula, G., & Iannone, F. (2018). Sarcopenia in Patients with Rheumatic Diseases: Prevalence and Associated Risk Factors. *Journal of Clinical Medicine*, *7*(12), 504. https://doi.org/10.3390/jcm7120504

Bartoloni, E., Alunno, A., Bistoni, O., & Gerli, R. (2010). How early is the atherosclerotic risk in rheumatoid arthritis? *Autoimmunity Reviews*, *9*(10), 701–707. https://doi.org/10.1016/j.autrev.2010.06.001

Beaudart, C., Dawson, A., Shaw, S. C., Harvey, N. C., Kanis, J. A., Binkley, N., Reginster, J. Y., Chapurlat, R., Chan, D. C., Bruyère, O., Rizzoli, R., Cooper, C., Dennison, E. M., & IOF-ESCEO Sarcopenia Working Group. (2017). Nutrition and physical activity in the prevention and treatment of sarcopenia: Systematic review. *Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *28*(6), 1817–1833. https://doi.org/10.1007/s00198-017-3980-9

Bijlsma, J. W., Hachulla, E., & European League against Rheumatism. (2015). *EULAR Textbook on Rheumatic Diseases*. London:BMJ.

Bissell, L.-A., Hensor, E. M. A., Kozera, L., Mackie, S. L., Burska, A. N., Nam, J. L., Keen, H., Villeneuve, E., Donica, H., Buch, M. H., Conaghan, P. G., Andrews, J., Emery, P., & Morgan, A. W. (2016). Improvement in insulin resistance is greater when infliximab is added to methotrexate during intensive treatment of early rheumatoid arthritis – Results from the IDEA study. *Rheumatology*, *55*(12), 2181–2190. https://doi.org/10.1093/rheumatology/kew306

Błyszczuk, P., & Szekanecz, Z. (2020). Pathogenesis of ischaemic and non-ischaemic heart diseases in rheumatoid arthritis. *RMD Open*, *6*(1). https://doi.org/10.1136/rmdopen-2019-001032

Book, C., Karlsson, M. K., Åkesson, K., & Jacobsson, L. T. H. (2009). Early rheumatoid arthritis and body composition. *Rheumatology*, *48*(9), 1128–1132. https://doi.org/10.1093/rheumatology/kep165

Book, C., Karlsson, M., Nilsson, J.-Å., Åkesson, K., & Jacobsson, L. (2011). Changes in body composition after 2 years with rheumatoid arthritis. *Scandinavian Journal of Rheumatology*, *40*(2), 95–100. https://doi.org/10.3109/03009742.2010.507215

Borst, S. E. (2004). The role of TNF-α in insulin resistance. *Endocrine*, *23*(2–3), 177–182.

Boulé, N. G., Haddad, E., Kenny, G. P., Wells, G. A., & Sigal, R. J. (2001). Effects of Exercise on Glycemic Control and Body Mass in Type 2 Diabetes Mellitus: A Meta-analysis of Controlled Clinical Trials. *JAMA*, *286*(10), 1218–1227. https://doi.org/10.1001/jama.286.10.1218

Boyer, J.-F., Gourraud, P.-A., Cantagrel, A., Davignon, J.-L., & Constantin, A. (2011). Traditional cardiovascular risk factors in rheumatoid arthritis: A meta-analysis. *Joint, Bone, Spine: Revue Du Rhumatisme*, *78*(2), 179–183. https://doi.org/10.1016/j.jbspin.2010.07.016

Burggraaf, B., van Breukelen – van der Stoep, D. F., de Vries, M. A., Klop, B., van Zeben, J., van de Geijn, G.-J. M., van der Meulen, N., Birnie, E., Prinzen, L., & Castro Cabezas, M. (2018). Progression of subclinical atherosclerosis in subjects with rheumatoid arthritis and the metabolic syndrome. *Atherosclerosis*, *271*, 84–91. https://doi.org/10.1016/j.atherosclerosis.2018.02.019

Burska, A. N., Sakthiswary, R., & Sattar, N. (2015). Effects of Tumour Necrosis Factor Antagonists on Insulin Sensitivity/Resistance in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *PLoS ONE*, *10*(6). https://doi.org/10.1371/journal.pone.0128889

Buttgereit, F., & Burmester, G. R. (2016). Rheumatoid arthritis: Glucocorticoid therapy and body composition. *Nature Reviews Rheumatology*, *12*(8), 444–445. https://doi.org/10.1038/nrrheum.2016.114

Cerhan, J. R., Saag, K. G., Criswell, L. A., Merlino, L. A., & Mikuls, T. R. (2002). Blood transfusion, alcohol use, and anthropometric risk factors for rheumatoid arthritis in older women. *The Journal of Rheumatology*, *29*(2), 246–254.

Challal, S., Minichiello, E., Boissier, M.-C., & Semerano, L. (2015). Cachexia and adiposity in rheumatoid arthritis. Relevance for disease management and clinical outcomes. *Joint Bone Spine*. https://doi.org/10.1016/j.jbspin.2015.04.010

Chehade, L., Jaafar, Z. A., El Masri, D., Zmerly, H., Kreidieh, D., Tannir, H., Itani, L., & El Ghoch, M. (2019). Lifestyle Modification in Rheumatoid Arthritis: Dietary and Physical Activity Recommendations Based on Evidence. *Current Rheumatology Reviews*. https://doi.org/10.2174/1573397115666190121135940

Chung, C. P., Oeser, A., Solus, J. F., Avalos, I., Gebretsadik, T., Shintani, A., Raggi, P., Sokka, T., Pincus, T., & Stein, C. M. (2008). Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. *Atherosclerosis*, *196*(2), 756–763. https://doi.org/10.1016/j.atherosclerosis.2007.01.004

Cleasby, M. E., Jamieson, P. M., & Atherton, P. J. (2016). Insulin resistance and sarcopenia: Mechanistic links between common co-morbidities. *Journal of Endocrinology*, *229*(2), R67–R81. https://doi.org/10.1530/JOE-15-0533

Combe, B., Landewe, R., Daien, C. I., Hua, C., Aletaha, D., Álvaro-Gracia, J. M., Bakkers, M., Brodin, N., Burmester, G. R., Codreanu, C., Conway, R., Dougados, M., Emery, P., Ferraccioli, G., Fonseca, J., Raza, K., Silva-Fernández, L., Smolen, J. S., Skingle, D., … Vollenhoven, R. van. (2017). 2016 update of the EULAR recommendations for the management of early arthritis. *Annals of the Rheumatic Diseases*, *76*(6), 948–959. https://doi.org/10.1136/annrheumdis-2016-210602

Cornelissen, V. A., & Smart, N. A. (2013). Exercise training for blood pressure: A systematic review and meta-analysis. *Journal of the American Heart Association*, *2*(1), e004473. https://doi.org/10.1161/JAHA.112.004473

Corrado, A., Colia, R., Rotondo, C., Sanpaolo, E., & Cantatore, F. P. (2019). Changes in serum adipokines profile and insulin resistance in patients with rheumatoid arthritis treated with anti-TNF-α. *Current Medical Research and Opinion*, *35*(12), 2197–2205. https://doi.org/10.1080/03007995.2019.1654988

Crowson, C. S., Gabriel, S. E., Semb, A. G., van Riel, P. L. C. M., Karpouzas, G., Dessein, P. H., Hitchon, C., Pascual-Ramos, V., Kitas, G. D., & Trans-Atlantic Cardiovascular Consortium for Rheumatoid Arthritis. (2017). Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: A validation analysis of patients from seven countries. *Rheumatology (Oxford, England)*, *56*(7), 1102–1110. https://doi.org/10.1093/rheumatology/kex038

Crowson, C. S., Myasoedova, E., Davis, J. M., Matteson, E. L., Roger, V. L., Therneau, T. M., Fitz-Gibbon, P., Rodeheffer, R. J., & Gabriel, S. E. (2011). Increased Prevalence of Metabolic Syndrome Associated with Rheumatoid Arthritis in Patients without Clinical Cardiovascular Disease. *The Journal of Rheumatology*, *38*(1), 29–35. https://doi.org/10.3899/jrheum.100346

Crowson, C. S., Rollefstad, S., Ikdahl, E., Kitas, G. D., Riel, P. L. C. M. van, Gabriel, S. E., Matteson, E. L., Kvien, T. K., Douglas, K., Sandoo, A., Arts, E., Wållberg-Jonsson, S., Innala, L., Karpouzas, G., Dessein, P. H., Tsang, L., El-Gabalawy, H., Hitchon, C., Ramos, V. P., … Semb, A. G. (2018). Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *77*(1), 48–54. https://doi.org/10.1136/annrheumdis-2017-211735

Cruz-Jentoft, A. J., Baeyens, J. P., Bauer, J. M., Boirie, Y., Cederholm, T., Landi, F., Martin, F. C., Michel, J.-P., Rolland, Y., Schneider, S. M., Topinková, E., Vandewoude, M., & Zamboni, M. (2010). Sarcopenia: European consensus on definition and diagnosis. *Age and Ageing*, *39*(4), 412–423. https://doi.org/10.1093/ageing/afq034

Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A. A., Schneider, S. M., Sieber, C. C., Topinkova, E., Vandewoude, M., Visser, M., Zamboni, M., People 2 (EWGSOP2), W. G. for the E. W. G. on S. in O., & Ewgsop2, and the E. G. for. (2019). Sarcopenia: Revised European consensus on definition and diagnosis. *Age and Ageing*, *48*(1), 16. https://doi.org/10.1093/ageing/afy169

Cutolo, M., Kitas, G. D., & van Riel, P. L. C. M. (2014). Burden of disease in treated rheumatoid arthritis patients: Going beyond the joint. *Seminars in Arthritis and Rheumatism*, *43*(4), 479–488. https://doi.org/10.1016/j.semarthrit.2013.08.004

Cutolo, M., & Nikiphorou, E. (2018). Don't neglect nutrition in rheumatoid arthritis! *RMD Open*, *4*(1), e000591. https://doi.org/10.1136/rmdopen-2017-000591

da Cunha, V. R., Brenol, C. V., Brenol, J. C. T., Fuchs, S. C., Arlindo, E. M., Melo, I. M. F., Machado, C. A., de Castro Chaves, H., & Xavier, R. M. (2012). Metabolic syndrome prevalence is increased in rheumatoid arthritis patients and is associated with disease activity. *Scandinavian Journal of Rheumatology*, *41*(3), 186–191. https://doi.org/10.3109/03009742.2011.626443

Dao, H.-H., Do, Q.-T., & Sakamoto, J. (2011). Abnormal body composition phenotypes in Vietnamese women with early rheumatoid arthritis. *Rheumatology*, *50*(7), 1250–1258. https://doi.org/10.1093/rheumatology/ker004

Dawson-Hughes, B., & Bischoff-Ferrari, H. (2016). Considerations concerning the definition of sarcopenia. *Osteoporosis International*, *27*(11), 3139–3144. https://doi.org/10.1007/s00198-016-3674-8

DeFronzo, R. A., & Ferrannini, E. (1991). Insulin Resistance: A Multifaceted Syndrome Responsible for NIDDM, Obesity, Hypertension, Dyslipidemia, and Atherosclerotic Cardiovascular Disease. *Diabetes Care*, *14*(3), 173–194. https://doi.org/10.2337/diacare.14.3.173

del Rincón, I., Polak, J. F., O'Leary, D. H., Battafarano, D. F., Erikson, J. M., Restrepo, J. F., Molina, E., & Escalante, A. (2015). Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *74*(6), 1118–1123. https://doi.org/10.1136/annrheumdis-2013-205058

Delgado-Frías, E., González-Gay, M. A., Muñiz-Montes, J. R., Gómez Rodríguez-Bethencourt, M. A., González-Díaz, A., Díaz-González, F., & Ferraz-Amaro, I. (2015). Relationship of abdominal adiposity and body composition with endothelial dysfunction in patients with rheumatoid arthritis. *Clinical and Experimental Rheumatology*, *33*(4), 516–523.

Dent, E., Morley, J. E., Cruz-Jentoft, A. J., Arai, H., Kritchevsky, S. B., Guralnik, J., Bauer, J. M., Pahor, M., Clark, B. C., Cesari, M., Ruiz, J., Sieber, C. C., Aubertin-Leheudre, M., Waters, D. L., Visvanathan, R., Landi, F., Villareal, D. T., Fielding, R., Won, C. W., … Vellas, B. (2018). International Clinical Practice Guidelines for Sarcopenia (ICFSR): Screening, Diagnosis and Management. *The Journal of Nutrition, Health & Aging*, *22*(10), 1148–1161. https://doi.org//10.1007/s12603-018-1139-9

Després, J.-P., Lamarche, B., Mauriège, P., Cantin, B., Dagenais, G. R., Moorjani, S., & Lupien, P.-J. (1996). Hyperinsulinemia as an Independent Risk Factor for Ischemic Heart Disease. *New England Journal of Medicine*, *334*(15), 952–958. https://doi.org/10.1056/NEJM199604113341504

Dessein, P. H., Joffe, B. I., Stanwix, A. E., Christian, B. F., & Veller, M. (2004). Glucocorticoids and insulin sensitivity in rheumatoid arthritis. *The Journal of Rheumatology*, *31*(5), 867–874.

Dessein, P. H., Tobias, M., & Veller, M. G. (2006). Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. *The Journal of Rheumatology*, *33*(12), 2425–2432.

Ding, C., Chan, Z., & Magkos, F. (2016). Lean, but not healthy: The "metabolically obese, normal-weight" phenotype. *Current Opinion in Clinical Nutrition and Metabolic Care*, *19*(6), 408–417. https://doi.org/10.1097/MCO.0000000000000317

Dubreuil, M., Rho, Y. H., Man, A., Zhu, Y., Zhang, Y., Love, T. J., Ogdie, A., Gelfand, J. M., & Choi, H. K. (2014). Diabetes incidence in psoriatic arthritis, psoriasis and rheumatoid arthritis: A UK population-based cohort study. *Rheumatology (Oxford, England)*, *53*(2), 346–352. https://doi.org/10.1093/rheumatology/ket343

Eckel, N., Mühlenbruch, K., Meidtner, K., Boeing, H., Stefan, N., & Schulze, M. B. (2015). Characterization of metabolically unhealthy normal-weight individuals: Risk factors and their associations with type 2 diabetes. *Metabolism*, *64*(8), 862–871. https://doi.org/10.1016/j.metabol.2015.03.009

Eckel, R. H., Grundy, S. M., & Zimmet, P. Z. (2005). The metabolic syndrome. *The Lancet*, *365*(9468), 1415–1428. https://doi.org/10.1016/S0140-6736(05)66378-7

Eddy, D., Schlessinger, L., Kahn, R., Peskin, B., & Schiebinger, R. (2009). Relationship of Insulin Resistance and Related Metabolic Variables to Coronary Artery Disease: A Mathematical Analysis. *Diabetes Care*, *32*(2), 361–366. https://doi.org/10.2337/dc08-0854

Eglit, T., Rajasalu, T., & Lember, M. (2012). Metabolic syndrome in estonia: Prevalence and associations with insulin resistance. *International Journal of Endocrinology*, *2012*, 951672. https://doi.org/10.1155/2012/951672

Eglit, T., Ringmets, I., & Lember, M. (2013). Obesity, High-Molecular-Weight (HMW) Adiponectin, and Metabolic Risk Factors: Prevalence and Gender-Specific Associations in Estonia. *PLOS ONE*, *8*(9), e73273. https://doi.org/10.1371/journal.pone.0073273

Elkan, A.-C., Håkansson, N., Frostegård, J., Cederholm, T., & Hafström, I. (2009). Rheumatoid cachexia is associated with dyslipidemia and low levels of atheroprotective natural antibodies against phosphorylcholine but not with dietary fat in patients with rheumatoid arthritis: A cross-sectional study. *Arthritis Research & Therapy*, *11*(2), R37. https://doi.org/10.1186/ar2643

England, B. R., Baker, J. F., Sayles, H., Michaud, K., Caplan, L., Davis, L. A., Cannon, G. W., Sauer, B. C., Solow, E. B., Reimold, A. M., Kerr, G. S., & Mikuls, T. R. (2018). Body Mass Index, Weight Loss, and Cause-Specific Mortality in Rheumatoid Arthritis. *Arthritis Care & Research*, *70*(1), 11–18. https://doi.org/10.1002/acr.23258

England, B. R., Sayles, H., Michaud, K., Caplan, L., Davis, L. A., Cannon, G. W., Sauer, B. C., Solow, E. B., Reimold, A. M., Kerr, G. S., Schwab, P., Baker, J. F., & Mikuls, T. R. (2016). Cause-Specific Mortality in Male US Veterans With Rheumatoid Arthritis. *Arthritis Care & Research*, *68*(1), 36–45. https://doi.org/10.1002/acr.22642

England, B. R., Thiele, G. M., Anderson, D. R., & Mikuls, T. R. (2018). Increased cardiovascular risk in rheumatoid arthritis: Mechanisms and implications. *The BMJ*, *361*. https://doi.org/10.1136/bmj.k1036

Engvall, I.-L., Elkan, A.-C., Tengstrand, B., Cederholm, T., Brismar, K., & Hafstrom, I. (2008). Cachexia in rheumatoid arthritis is associated with inflammatory activity, physical disability, and low bioavailable insulin-like growth factor. *Scandinavian Journal of Rheumatology*, *37*(5), 321–328. https://doi.org/10.1080/03009740802055984

Escalante A, Haas RW, & del Rincón I. (2005). Paradoxical effect of body mass index on survival in rheumatoid arthritis: Role of comorbidity and systemic inflammation. *Archives of Internal Medicine*, *165*(14), 1624–1629. https://doi.org/10.1001/archinte.165.14.1624

Evans, W. J., Morley, J. E., Argilés, J., Bales, C., Baracos, V., Guttridge, D., Jatoi, A., Kalantar-Zadeh, K., Lochs, H., Mantovani, G., Marks, D., Mitch, W. E., Muscaritoli, M., Najand, A., Ponikowski, P., Fanelli, F. R., Schambelan, M., Schols, A., Schuster, M., … Anker, S. D. (2008). Cachexia: A new definition. *Clinical Nutrition*, *27*(6), 793–799. https://doi.org/10.1016/j.clnu.2008.06.013

Ferrannini, E., Natali, A., Bell, P., Cavallo-Perin, P., Lalic, N., & Mingrone, G. (1997). Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). *The Journal of Clinical Investigation*, *100*(5), 1166–1173. https://doi.org/10.1172/JCI119628

Ferraz-Amaro, I., González-Juanatey, C., López-Mejias, R., Riancho-Zarrabeitia, L., & González-Gay, M. A. (2013). Metabolic Syndrome in Rheumatoid Arthritis. *Mediators of Inflammation*, *2013*. https://doi.org/10.1155/2013/710928

Galassi, A., Reynolds, K., & He, J. (2006). Metabolic Syndrome and Risk of Cardiovascular Disease: A Meta-Analysis. *The American Journal of Medicine*, *119*(10), 812–819. https://doi.org/10.1016/j.amjmed.2006.02.031

Gallagher, L., Cregan, S., Biniecka, M., Cunningham, C., Veale, D. J., Kane, D. J., Fearon, U., & Mullan, R. H. (2019). Insulin Resistant Pathways are associated with

Disease Activity in Rheumatoid Arthritis and are Subject to Disease Modification through Metabolic Reprogramming; A Potential Novel Therapeutic Approach. *Arthritis & Rheumatology*, *n/a*(n/a). https://doi.org/10.1002/art.41190

Gast, K. B., Tjeerdema, N., Stijnen, T., Smit, J. W. A., & Dekkers, O. M. (2012). Insulin Resistance and Risk of Incident Cardiovascular Events in Adults without Diabetes: Meta-Analysis. *PLoS ONE*, *7*(12). https://doi.org/10.1371/journal.pone.0052036

Geer, E. B., & Shen, W. (2009). Gender Differences in Insulin Resistance, Body Composition, and Energy Balance. *Gender Medicine*, *6*(Suppl 1), 60–75. https://doi.org/10.1016/j.genm.2009.02.002

Geirsdottir, O. G., Arnarson, A., Ramel, A., Jonsson, P. V., & Thorsdottir, I. (2013). Dietary protein intake is associated with lean body mass in community-dwelling older adults. *Nutrition Research*, *33*(8), 608–612. https://doi.org/10.1016/j.nutres.2013.05.014

George, M. D., & Baker, J. F. (2016). The Obesity Epidemic and Consequences for Rheumatoid Arthritis Care. *Current Rheumatology Reports*, *18*(1), 6. https://doi.org/10.1007/s11926-015-0550-z

George, M. D., Giles, J. T., Katz, P. P., England, B. R., Mikuls, T. R., Michaud, K., Ogdie-Beatty, A. R., Ibrahim, S., Cannon, G. W., Caplan, L., Sauer, B. C., & Baker, J. F. (2017). Impact of Obesity and Adiposity on Inflammatory Markers in Patients With Rheumatoid Arthritis. *Arthritis Care & Research*. https://doi.org/10.1002/acr.23229

Giles, J. T. (2019). Extra-articular Manifestations and Comorbidity in Rheumatoid Arthritis: Potential Impact of Pre–Rheumatoid Arthritis Prevention. *Clinical Therapeutics*, *41*(7), 1246–1255. https://doi.org/10.1016/j.clinthera.2019.04.018

Giles, J. T., Allison, M., Blumenthal, R. S., Post, W., Gelber, A. C., Petri, M., Tracy, R., Szklo, M., & Bathon, J. M. (2010). Abdominal adiposity in rheumatoid arthritis: Association with cardiometabolic risk factors and disease characteristics. *Arthritis & Rheumatism*, *62*(11), 3173–3182. https://doi.org/10.1002/art.27629

Giles, J. T., Bartlett, S. J., Andersen, R. E., Fontaine, K. R., & Bathon, J. M. (2008). Association of Body Composition With Disability in Rheumatoid Arthritis: Impact of Appendicular Fat and Lean Tissue Mass. *Arthritis and Rheumatism*, *59*(10), 1407–1415. https://doi.org/10.1002/art.24109

Giles, J. T., Danielides, S., Szklo, M., Post, W. S., Blumenthal, R. S., Petri, M., Schreiner, P. J., Budoff, M., Detrano, R., & Bathon, J. M. (2015). Insulin Resistance in Rheumatoid Arthritis: Disease-Related Indicators and Associations With the Presence and Progression of Subclinical Atherosclerosis. *Arthritis & Rheumatology*, *67*(3), 626–636. https://doi.org/10.1002/art.38986

Giles, J. T., Ling, S. M., Ferrucci, L., Bartlett, S. J., Andersen, R. E., Towns, M., Muller, D., Fontaine, K. R., & Bathon, J. M. (2008). Abnormal Body Composition Phenotypes in Older Rheumatoid Arthritis Patients: Association With Disease Characteristics and Pharmacotherapies. *Arthritis and Rheumatism*, *59*(6), 807–815. https://doi.org/10.1002/art.23719

Gonzalez, A., Maradit Kremers, H., Crowson, C. S., Ballman, K. V., Roger, V. L., Jacobsen, S. J., O'Fallon, W. M., & Gabriel, S. E. (2008). Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? *Annals of the Rheumatic Diseases*, *67*(1), 64–69. https://doi.org/10.1136/ard.2006.059980

Gonzalez-Gay, M. A., De Matias, J. M., Gonzalez-Juanatey, C., Garcia-Porrua, C., Sanchez-Andrade, A., Martin, J., & Llorca, J. (2006). Anti-tumor necrosis factor-

alpha blockade improves insulin resistance in patients with rheumatoid arthritis. *Clinical and Experimental Rheumatology*, *24*(1), 83–86.

González-Gay, M. A., Llorca, J., González-Juanatey, C., & Dessein, P. H. (2015). Is the Homeostatic Model Assessment of Insulin Resistance a Poor Predictor of Cardiovascular Disease in Rheumatoid Arthritis? Comment on the Article by Giles et al. *Arthritis & Rheumatology*, *67*(9), 2548–2550. https://doi.org/10.1002/art.39222

Goodson, N. J., Silman, A. J., Pattison, D. J., Lunt, M., Bunn, D., Luben, R., Day, N., Khaw, K.-T., & Symmons, D. P. M. (2004). Traditional cardiovascular risk factors measured prior to the onset of inflammatory polyarthritis. *Rheumatology*, *43*(6), 731–736. https://doi.org/10.1093/rheumatology/keh161

Grundy, S. M., Brewer, H. B., Cleeman, J. I., Smith, S. C., Lenfant, C., & Participants, for the C. (2004). Definition of Metabolic Syndrome Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation*, *109*(3), 433–438. https://doi.org/10.1161/01.CIR.0000111245.75752.C6

Guin, A., Sinhamahapatra, P., Misra, S., Choudhury Mazumder, S. R., Chatterjee, S., & Ghosh, A. (2019). Incidence and effect of insulin resistance on progression of atherosclerosis in rheumatoid arthritis patients of long disease duration. *Biomedical Journal*, *42*(6), 394–402. https://doi.org/10.1016/j.bj.2019.01.007

Hallajzadeh, J., Safiri, S., Mansournia, M. A., Khoramdad, M., Izadi, N., Almasi-Hashiani, A., Pakzad, R., Ayubi, E., Sullman, M. J. M., & Karamzad, N. (2017). Metabolic syndrome and its components among rheumatoid arthritis patients: A comprehensive updated systematic review and meta-analysis. *PLoS ONE*, *12*(3). https://doi.org/10.1371/journal.pone.0170361

Halm, V. P. van, Nielen, M. M. J., Nurmohamed, M. T., Schaardenburg, D. van, Reesink, H. W., Voskuyl, A. E., Twisk, J. W. R., Stadt, R. J. van de, Koning, M. H. M. T. de, Habibuw, M. R., Horst–Bruinsma, I. E. van der, & Dijkmans, B. a. C. (2007). Lipids and inflammation: Serial measurements of the lipid profile of blood donors who later developed rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *66*(2), 184–188. https://doi.org/10.1136/ard.2006.051672

Hannawi, S., Haluska, B., Marwick, T. H., & Thomas, R. (2007). Atherosclerotic disease is increased in recent-onset rheumatoid arthritis: A critical role for inflammation. *Arthritis Research & Therapy*, *9*(6), R116. https://doi.org/10.1186/ar2323

Hedström, A. K., Stawiarz, L., Klareskog, L., & Alfredsson, L. (2018). Smoking and susceptibility to rheumatoid arthritis in a Swedish population-based case–control study. *European Journal of Epidemiology*, *33*(4), 415–423. https://doi.org/10.1007/s10654-018-0360-5

Heimans, L., van den Broek, M., le Cessie, S., Siegerink, B., Riyazi, N., Han, K. H., Kerstens, P. J. S. M., Huizinga, T. W. J., Lems, W. F., & Allaart, C. F. (2013). Association of high body mass index with decreased treatment response to combination therapy in recent-onset rheumatoid arthritis patients. *Arthritis Care & Research*, *65*(8), 1235–1242. https://doi.org/10.1002/acr.21978

Hernández Avila, M., Liang, M. H., Willett, W. C., Stampfer, M. J., Colditz, G. A., Rosner, B., Roberts, W. N., Hennekens, C. H., & Speizer, F. E. (1990). Reproductive factors, smoking, and the risk for rheumatoid arthritis. *Epidemiology (Cambridge, Mass.)*, *1*(4), 285–291. https://doi.org/10.1097/00001648-199007000-00005

Hernández-Hernández, V., Ferraz-Amaro, I., & Díaz-González, F. (2014). Influence of disease activity on the physical activity of rheumatoid arthritis patients. *Rheumatology (Oxford, England)*, *53*(4), 722–731. https://doi.org/10.1093/rheumatology/ket422

Higgins, S. C., Adams, J., & Hughes, R. (2018). Measuring hand grip strength in rheumatoid arthritis. *Rheumatology International*, *38*(5), 707–714. https://doi.org/10.1007/s00296-018-4024-2

Hippisley-Cox, J., Coupland, C., Vinogradova, Y., Robson, J., Minhas, R., Sheikh, A., & Brindle, P. (2008). Predicting cardiovascular risk in England and Wales: Prospective derivation and validation of QRISK2. *BMJ : British Medical Journal*, *336*(7659), 1475–1482. https://doi.org/10.1136/bmj.39609.449676.25

Hollan, I., Ronda, N., Dessein, P., Agewall, S., Karpouzas, G., Tamargo, J., Niessner, A., Savarese, G., Rosano, G., Kaski, J. C., Wassmann, S., & Meroni, P. L. (2019). Lipid management in rheumatoid arthritis: A position paper of the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *European Heart Journal – Cardiovascular Pharmacotherapy*. https://doi.org/10.1093/ehjcvp/pvz033

Holmqvist, M., Ljung, L., & Askling, J. (2018). Mortality following new-onset Rheumatoid Arthritis: Has modern Rheumatology had an impact? *Annals of the Rheumatic Diseases*, *77*(1), 85–91. https://doi.org/10.1136/annrheumdis-2017-212131

Hong, S., & Choi, K. M. (2020). Sarcopenic Obesity, Insulin Resistance, and Their Implications in Cardiovascular and Metabolic Consequences. *International Journal of Molecular Sciences*, *21*(2), 494. https://doi.org/10.3390/ijms21020494

Humphreys, J. H., Warner, A., Chipping, J., Marshall, T., Lunt, M., Symmons, D. P. M., & Verstappen, S. M. M. (2014). Mortality Trends in Patients With Early Rheumatoid Arthritis Over 20 Years: Results From the Norfolk Arthritis Register: Trends of Mortality Rates in UK Patients With Early RA. *Arthritis Care & Research*, *66*(9), 1296–1301. https://doi.org/10.1002/acr.22296

Huxley, R., Mendis, S., Zheleznyakov, E., Reddy, S., & Chan, J. (2010). Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk – A review of the literature. *European Journal of Clinical Nutrition*, *64*(1), 16–22. https://doi.org/10.1038/ejcn.2009.68

Ikdahl, E., Wibetoe, G., Rollefstad, S., Salberg, A., Bergsmark, K., Kvien, T. K., Olsen, I. C., Soldal, D. M., Bakland, G., Lexberg, Å., Fevang, B. T. S., Gulseth, H. C., Haugeberg, G., & Semb, A. G. (2019). Guideline recommended treatment to targets of cardiovascular risk is inadequate in patients with inflammatory joint diseases. *International Journal of Cardiology*, *274*, 311–318. https://doi.org/10.1016/j.ijcard.2018.06.111

Isomaa, B., Almgren, P., Tuomi, T., Forsén, B., Lahti, K., Nissén, M., Taskinen, M.-R., & Groop, L. (2001). Cardiovascular Morbidity and Mortality Associated With the Metabolic Syndrome. *Diabetes Care*, *24*(4), 683–689. https://doi.org/10.2337/diacare.24.4.683

Johnson, A. M. F., & Olefsky, J. M. (2013). The Origins and Drivers of Insulin Resistance. *Cell*, *152*(4), 673–684. https://doi.org/10.1016/j.cell.2013.01.041

Kalyani, R. R., Corriere, M., & Ferrucci, L. (2014). Age-related and disease-related muscle loss: The effect of diabetes, obesity, and other diseases. *The Lancet. Diabetes & Endocrinology*, *2*(10), 819–829. https://doi.org/10.1016/S2213-8587(14)70034-8

Karimi, M., Mazloomzadeh, S., Kafan, S., & Amirmoghadami, H. (2011). The frequency of metabolic syndrome in women with rheumatoid arthritis and in controls. *International Journal of Rheumatic Diseases*, *14*(3), 248–254. https://doi.org/10.1111/j.1756-185X.2011.01595.x

Katz, P. (2017). Causes and consequences of fatigue in rheumatoid arthritis. *Current Opinion in Rheumatology*, *29*(3), 269–276. https://doi.org/10.1097/BOR.0000000000000376

Kerekes, G., Nurmohamed, M. T., González-Gay, M. A., Seres, I., Paragh, G., Kardos, Z., Baráth, Z., Tamási, L., Soltész, P., & Szekanecz, Z. (2014). Rheumatoid arthritis and metabolic syndrome. *Nature Reviews Rheumatology*, *10*(11), 691–696. https://doi.org/10.1038/nrrheum.2014.121

Kerola, A. M., Kauppi, M. J., Kerola, T., & Nieminen, T. V. M. (2012). How early in the course of rheumatoid arthritis does the excess cardiovascular risk appear? *Annals of the Rheumatic Diseases*, *71*(10), 1606–1615. https://doi.org/10.1136/annrheumdis-2012-201334

Kerola, A. M., Nieminen, T. V. M., Virta, L. J., Kautiainen, H., Kerola, T., Pohjolainen, T., Kauppi, M. J., & Puolakka, K. (2015). No increased cardiovascular mortality among early rheumatoid arthritis patients: A nationwide register study in 2000–2008. *Clinical and Experimental Rheumatology*, *33*(3), 391–398.

Konijn, N. P. C., Tuyl, V., D, L. H., Boers, M., Ven, V. D., M, P., den Uyl, D., Wee, T., M, M., Kerstens, P., Voskuyl, A. E., van Schaardenburg, D., Lems, W. F., & Nurmohamed, M. T. (2016). The short-term effects of two high-dose, step-down prednisolone regimens on body composition in early rheumatoid arthritis. *Rheumatology*, *55*(9), 1615–1622. https://doi.org/10.1093/rheumatology/kew221

Kuriya, B., Schieir, O., Valois, M. F., Pope, J. E., Boire, G., Bessette, L., Hazlewood, G., Thorne, J. C., Tin, D., Hitchon, C., Bartlett, S., Keystone, E. C., Bykerk, V. P., & Barra, L. (2019). Prevalence and Characteristics of Metabolic Syndrome Differ in Men and Women with Early Rheumatoid Arthritis. *Acr Open Rheumatology*, *1*(9), 535–541. https://doi.org/10.1002/acr2.11075

Laakso, M. (2015). Is Insulin Resistance a Feature of or a Primary Risk Factor for Cardiovascular Disease? *Current Diabetes Reports*, *15*(12), 105. https://doi.org/10.1007/s11892-015-0684-4

Laakso, M., & Kuusisto, J. (2014). Insulin resistance and hyperglycaemia in cardiovascular disease development. *Nature Reviews Endocrinology*, *10*(5), 293–302. https://doi.org/10.1038/nrendo.2014.29

Lacaille, D., Avina-Zubieta, J. A., Sayre, E. C., & Abrahamowicz, M. (2017). Improvement in 5-year mortality in incident rheumatoid arthritis compared with the general population-closing the mortality gap. *Annals of the Rheumatic Diseases*, *76*(6), 1057–1063. https://doi.org/10.1136/annrheumdis-2016-209562

Lahiri, M., Luben, R. N., Morgan, C., Bunn, D. K., Marshall, T., Lunt, M., Verstappen, S. M. M., Symmons, D. P. M., Khaw, K.-T., Wareham, N., & Bruce, I. N. (2014). Using lifestyle factors to identify individuals at higher risk of inflammatory polyarthritis (results from the European Prospective Investigation of Cancer-Norfolk and the Norfolk Arthritis Register – The EPIC-2-NOAR Study). *Annals of the Rheumatic Diseases*, *73*(1), 219–226. https://doi.org/10.1136/annrheumdis-2012-202481

Lee, C. M. Y., Huxley, R. R., Wildman, R. P., & Woodward, M. (2008). Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: A meta-analysis. *Journal of Clinical Epidemiology*, *61*(7), 646–653. https://doi.org/10.1016/j.jclinepi.2007.08.012

Lee, I.-M., Shiroma, E. J., Lobelo, F., Puska, P., Blair, S. N., & Katzmarzyk, P. T. (2012). Impact of Physical Inactivity on the World's Major Non-Communicable Diseases. *Lancet*, *380*(9838), 219–229. https://doi.org/10.1016/S0140-6736(12)61031-9

Lemmey, A. B., Ahmad, Y. A., School of Sport, Health & Exercise Sciences, Bangor University, Bangor, UK, & Research Institute for Sport & Exercise Sciences, Liverpool John Moores University, Liverpool, UK. (2018). Muscle loss following a single high-dose intramuscular injection of corticosteroids to treat disease flare in patients with rheumatoid arthritis. *European Journal of Rheumatology*, *5*(3), 160–164. https://doi.org/10.5152/eurjrheum.2018.17148

Lemmey, A. B., Marcora, S. M., Chester, K., Wilson, S., Casanova, F., & Maddison, P. J. (2009). Effects of high-intensity resistance training in patients with rheumatoid arthritis: A randomized controlled trial. *Arthritis Care & Research*, *61*(12), 1726–1734. https://doi.org/10.1002/art.24891

Lemmey, A. B., Wilkinson, T. J., Clayton, R. J., Sheikh, F., Whale, J., Jones, H. S. J., Ahmad, Y. A., Chitale, S., Jones, J. G., Maddison, P. J., & O'Brien, T. D. (2016). Tight control of disease activity fails to improve body composition or physical function in rheumatoid arthritis patients. *Rheumatology*, *55*(10), 1736–1745. https://doi.org/10.1093/rheumatology/kew243

Levitsky, A., Brismar, K., Hafström, I., Hambardzumyan, K., Lourdudoss, C., van Vollenhoven, R. F., & Saevarsdottir, S. (2017). Obesity is a strong predictor of worse clinical outcomes and treatment responses in early rheumatoid arthritis: Results from the SWEFOT trial. *RMD Open*, *3*(2), e000458. https://doi.org/10.1136/rmdopen-2017-000458

Liao, K. P., & Solomon, D. H. (2013). Traditional cardiovascular risk factors, inflammation and cardiovascular risk in rheumatoid arthritis. *Rheumatology*, *52*(1), 45–52. https://doi.org/10.1093/rheumatology/kes243

Liu, Y., Hazlewood, G. S., Kaplan, G. G., Eksteen, B., & Barnabe, C. (2017). Impact of Obesity on Remission and Disease Activity in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Arthritis Care & Research*, *69*(2), 157–165. https://doi.org/10.1002/acr.22932

Ljung, L., & Rantapää-Dahlqvist, S. (2016). Abdominal obesity, gender and the risk of rheumatoid arthritis – a nested case–control study. *Arthritis Research & Therapy*, *18*. https://doi.org/10.1186/s13075-016-1171-2

Mann, S., Beedie, C., & Jimenez, A. (2014). Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: Review, synthesis and recommendations. *Sports Medicine (Auckland, N.Z.)*, *44*(2), 211–221. https://doi.org/10.1007/s40279-013-0110-5

Manrique-Arija, S., Ureña, I., Valdivielso, P., Rioja, J., Jiménez-Núñez, F. G., Irigoyen, M. V., & Fernández-Nebro, A. (2015). Insulin resistance and levels of adipokines in patients with untreated early rheumatoid arthritis. *Clinical Rheumatology*. https://doi.org/10.1007/s10067-015-3106-8

Mantel, Ä., Holmqvist, M., Nyberg, F., Tornling, G., Frisell, T., Alfredsson, L., & Askling, J. (2015). Risk factors for the rapid increase in risk of acute coronary events in patients with new-onset rheumatoid arthritis: A nested case-control study. *Arthritis & Rheumatology (Hoboken, N.J.)*, *67*(11), 2845–2854. https://doi.org/10.1002/art.39267

Maradit-Kremers, H., Crowson, C. S., Nicola, P. J., Ballman, K. V., Roger, V. L., Jacobsen, S. J., & Gabriel, S. E. (2005). Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: A population-based cohort study. *Arthritis & Rheumatism*, *52*(2), 402–411. https://doi.org/10.1002/art.20853

Marcora, S., Lemmey, A., & Maddison, P. (2005). Dietary treatment of rheumatoid cachexia with β-hydroxy-β-methylbutyrate, glutamine and arginine: A randomised controlled trial. *Clinical Nutrition*, *24*(3), 442–454. https://doi.org/10.1016/j.clnu.2005.01.006

Marcora, S. M., Chester, K. R., Mittal, G., Lemmey, A. B., & Maddison, P. J. (2006). Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. *The American Journal of Clinical Nutrition*, *84*(6), 1463–1472. https://doi.org/10.1093/ajcn/84.6.1463

Marouen, S., Barnetche, T., Combe, B., Morel, J., & Daïen, C. I. (2017). TNF inhibitors increase fat mass in inflammatory rheumatic disease: A systematic review with meta-analysis. *Clinical and Experimental Rheumatology*, *35*(2), 337–343.

Martinez, K. E., Tucker, L. A., Bailey, B. W., & LeCheminant, J. D. (2017). *Expanded Normal Weight Obesity and Insulin Resistance in US Adults of the National Health and Nutrition Examination Survey* [Research Article]. Journal of Diabetes Research. https://doi.org/10.1155/2017/9502643

Marzetti, E., Calvani, R., Tosato, M., Cesari, M., Di Bari, M., Cherubini, A., Collamati, A., D'Angelo, E., Pahor, M., Bernabei, R., Landi, F., & on behalf of the SPRINTT Consortium. (2017). Sarcopenia: An overview. *Aging Clinical and Experimental Research*, *29*(1), 11–17. https://doi.org/10.1007/s40520-016-0704-5

Mathew, H., Farr, O. M., & Mantzoros, C. S. (2016). Metabolic health and weight: Understanding metabolically unhealthy normal weight or metabolically healthy obese patients. *Metabolism*, *65*(1), 73–80. https://doi.org/10.1016/j.metabol.2015.10.019

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*, *28*(7), 412–419.

Meek, I. L., Vonkeman, H. E., & van de Laar, M. A. F. J. (2014). Cardiovascular case fatality in rheumatoid arthritis is decreasing; first prospective analysis of a current low disease activity rheumatoid arthritis cohort and review of the literature. *BMC Musculoskeletal Disorders*, *15*, 142. https://doi.org/10.1186/1471-2474-15-142

Metsios, G. S., Moe, R. H., van der Esch, M., van Zanten, J. J. C. S. V., Fenton, S. A. M., Koutedakis, Y., Vitalis, P., Kennedy, N., Brodin, N., Bostrom, C., Swinnen, T. W., Tzika, K., Niedermann, K., Nikiphorou, E., Fragoulis, G. E., Vlieland, T. P. V. M., Van den Ende, C. H. M., Kitas, G. D., & The IMPACT-RMD Consortium. (2019). The effects of exercise on cardiovascular disease risk factors and cardiovascular physiology in rheumatoid arthritis. *Rheumatology International*. https://doi.org/10.1007/s00296-019-04483-6

Mirjafari, H., Farragher, T. M., Verstappen, S. M., Yates, A., Bunn, D., Marshall, T., Lunt, M., Symmons, D. P., & Bruce, I. N. (2011). Seropositivity is associated with insulin resistance in patients with early inflammatory polyarthritis: Results from the Norfolk Arthritis Register (NOAR): an observational study. *Arthritis Research & Therapy*, *13*(5), R159. https://doi.org/10.1186/ar3476

Mok, C. C., Ko, G. T. C., Ho, L. Y., Yu, K. L., Chan, P. T., & To, C. H. (2011). Prevalence of atherosclerotic risk factors and the metabolic syndrome in patients with chronic inflammatory arthritis. *Arthritis Care & Research*, *63*(2), 195–202. https://doi.org/10.1002/acr.20363

Montagna, G. L., Cacciapuoti, F., Buono, R., Manzella, D., Mennillo, G. A., Arciello, A., Valentini, G., & Paolisso, G. (2007). Insulin resistance is an independent risk factor

for atherosclerosis in rheumatoid arthritis. *Diabetes and Vascular Disease Research*, *4*(2), 130–135. https://doi.org/10.3132/dvdr.2007.031

Morović-Vergles, J., Salamon, L., Marasović-Krstulović, D., Kehler, T., Sakić, D., Badovinac, O., Vlak, T., Novak, S., Stiglić-Rogoznica, N., Hanih, M., Bedeković, D., Grazio, S., Kadojić, M., Milas-Ahić, J., Prus, V., Stamenković, D., Sošo, D., Anić, B., Babić-Naglić, D., & Gamulin, S. (2013). Is the prevalence of arterial hypertension in rheumatoid arthritis and osteoarthritis associated with disease? *Rheumatology International*, *33*(5), 1185–1192. https://doi.org/10.1007/s00296-012-2522-1

Morsley, K., Berntzen, B., Erwood, L., Bellerby, T., & Williamson, L. (2018). Progressive resistance training (PRT) improves rheumatoid arthritis outcomes: A district general hospital (DGH) model. *Musculoskeletal Care*, *16*(1), 13–17. https://doi.org/10.1002/msc.1193

Mottillo, S., Filion, K. B., Genest, J., Joseph, L., Pilote, L., Poirier, P., Rinfret, S., Schiffrin, E. L., & Eisenberg, M. J. (2010). The Metabolic Syndrome and Cardiovascular Risk: A Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology*, *56*(14), 1113–1132. https://doi.org/10.1016/j.jacc.2010.05.034

Myasoedova, E., Crowson, C. S., Kremers, H. M., Fitz-Gibbon, P. D., Therneau, T. M., & Gabriel, S. E. (2010). Total cholesterol and LDL levels decrease before rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *69*(7), 1310–1314. https://doi.org/10.1136/ard.2009.122374

Myasoedova, E., Crowson, C. S., Matteson, E. L., Davis, J. M., Therneau, T. M., & Gabriel, S. E. (2017). Decreased Cardiovascular Mortality in Patients with Incident Rheumatoid Arthritis (RA) in Recent Years: Dawn of a New Era in Cardiovascular Disease in RA? *The Journal of Rheumatology*, *44*(6), 732–739. https://doi.org/10.3899/jrheum.161154

National Institute for Health Development. (n.d.). *NutriData Food Composition Database*. Retrieved March 2, 2018, from tka.nutridata.ee

Nicolau, J., Lequerré, T., Bacquet, H., & Vittecoq, O. (2017). Rheumatoid arthritis, insulin resistance, and diabetes. *Joint Bone Spine*, *84*(4), 411–416. https://doi.org/10.1016/j.jbspin.2016.09.001

Nocon, M., Hiemann, T., Müller-Riemenschneider, F., Thalau, F., Roll, S., & Willich, S. N. (2008). Association of physical activity with all-cause and cardiovascular mortality: A systematic review and meta-analysis. *European Journal of Cardiovascular Prevention & Rehabilitation*, *15*(3), 239–246. https://doi.org/10.1097/HJR.0b013e3282f55e09

Nurmohamed, M. T., Heslinga, M., & Kitas, G. D. (2015). Cardiovascular comorbidity in rheumatic diseases. *Nature Reviews Rheumatology*, *advance online publication*. https://doi.org/10.1038/nrrheum.2015.112

Osthoff, A.-K. R., Niedermann, K., Braun, J., Adams, J., Brodin, N., Dagfinrud, H., Duruoz, T., Esbensen, B. A., Günther, K.-P., Hurkmans, E., Juhl, C. B., Kennedy, N., Kiltz, U., Knittle, K., Nurmohamed, M., Pais, S., Severijns, G., Swinnen, T. W., Pitsillidou, I. A., … Vlieland, T. P. M. V. (2018). 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Annals of the Rheumatic Diseases*, *77*(9), 1251–1260. https://doi.org/10.1136/annrheumdis-2018-213585

Paget, J. (1873). Clinical Lectures: ON THE NERVOUS MIMICRY OF ORGANIC DISEASES,. *The Lancet*, *102*(2616), 547–549. https://doi.org/10.1016/S0140-6736(02)69528-5

Pamuk, O. N., Unlü, E., & Cakir, N. (2006). Role of insulin resistance in increased frequency of atherosclerosis detected by carotid ultrasonography in rheumatoid arthritis. *The Journal of Rheumatology*, *33*(12), 2447–2452.

Panoulas, V. F., Metsios, G. S., Pace, A. V., John, H., Treharne, G. J., Banks, M. J., & Kitas, G. D. (2008). Hypertension in rheumatoid arthritis. *Rheumatology*, *47*(9), 1286–1298. https://doi.org/10.1093/rheumatology/ken159

Pappas, D. A., Nyberg, F., Kremer, J. M., Lampl, K., Reed, G. W., Horne, L., Ho, M., Onofrei, A., Malaviya, A. N., Rillo, O. L., Radominski, S. C., Gal, J., Gibofsky, A., Popkova, T. V., Laurindo, L., Kerzberg, E. M., Zahora, R., Pons-Estel, B. A., Curtis, J. R., … Greenberg, J. D. (2018). Prevalence of cardiovascular disease and major risk factors in patients with rheumatoid arthritis: A multinational cross-sectional study. *Clinical Rheumatology*, *37*(9), 2331–2340. https://doi.org/10.1007/s10067-018-4113-3

Patel, T. P., Rawal, K., Bagchi, A. K., Akolkar, G., Bernardes, N., Dias, D. da S., Gupta, S., & Singal, P. K. (2016). Insulin resistance: An additional risk factor in the pathogenesis of cardiovascular disease in type 2 diabetes. *Heart Failure Reviews*, *21*(1), 11–23. https://doi.org/10.1007/s10741-015-9515-6

Pedersen, M., Jacobsen, S., Klarlund, M., Pedersen, B. V., Wiik, A., Wohlfahrt, J., & Frisch, M. (2006). Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. *Arthritis Research & Therapy*, *8*(4), R133. https://doi.org/10.1186/ar2022

Peters, M. J. L., Symmons, D. P. M., McCarey, D., Dijkmans, B. A. C., Nicola, P., Kvien, T. K., McInnes, I. B., Haentzschel, H., Gonzalez-Gay, M. A., Provan, S., & others. (2010). EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Annals of the Rheumatic Diseases*, *69*(2), 325–331.

Petersson, S., Philippou, E., Rodomar, C., & Nikiphorou, E. (2018). The Mediterranean diet, fish oil supplements and Rheumatoid arthritis outcomes: Evidence from clinical trials. *Autoimmunity Reviews*, *17*(11), 1105–1114. https://doi.org/10.1016/j.autrev.2018.06.007

Piepoli, M. F., Hoes, A. W., Agewall, S., Albus, C., Brotons, C., Catapano, A. L., Cooney, M.-T., Corrà, U., Cosyns, B., Deaton, C., Graham, I., Hall, M. S., Hobbs, F. D. R., Løchen, M.-L., Löllgen, H., Marques-Vidal, P., Perk, J., Prescott, E., Redon, J., … Gale, C. (2016). 2016 European Guidelines on cardiovascular disease prevention in clinical practiceThe Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European Heart Journal*, *37*(29), 2315–2381. https://doi.org/10.1093/eurheartj/ehw106

Prete, M., Racanelli, V., Digiglio, L., Vacca, A., Dammacco, F., & Perosa, F. (2011). Extra-articular manifestations of rheumatoid arthritis: An update. *Autoimmunity Reviews*, *11*(2), 123–131. https://doi.org/10.1016/j.autrev.2011.09.001

Prospective Studies Collaboration. (2009). Body-mass index and cause-specific mortality in 900 000 adults: Collaborative analyses of 57 prospective studies. *The Lancet*, *373*(9669), 1083–1096. https://doi.org/10.1016/S0140-6736(09)60318-4

Pujades-Rodriguez, M., Duyx, B., Thomas, S. L., Stogiannis, D., Rahman, A., Smeeth, L., & Hemingway, H. (2016). Rheumatoid Arthritis and Incidence of Twelve Initial Presentations of Cardiovascular Disease: A Population Record-Linkage Cohort Study in England. *PLoS ONE*, *11*(3). https://doi.org/10.1371/journal.pone.0151245

Pyöräla, K. (1979). Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: Results from two population studies in Finland. *Diabetes Care*, *2*(2), 131–141.

Qin, B., Yang, M., Fu, H., Ma, N., Wei, T., Tang, Q., Hu, Z., Liang, Y., Yang, Z., & Zhong, R. (2015). Body mass index and the risk of rheumatoid arthritis: A systematic review and dose-response meta-analysis. *Arthritis Research & Therapy*, *17*, 86. https://doi.org/10.1186/s13075-015-0601-x

Rall, L. C., & Roubenoff, R. (2004). Rheumatoid cachexia: Metabolic abnormalities, mechanisms and interventions. *Rheumatology*, *43*(10), 1219–1223. https://doi.org/10.1093/rheumatology/keh321

Rao, P. M., Kelly, D. M., & Jones, T. H. (2013). Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. *Nature Reviews Endocrinology*, *9*(8), 479–493. https://doi.org/10.1038/nrendo.2013.122

Rodríguez, L. A. G., Tolosa, L. B., Ruigómez, A., Johansson, S., & Wallander, M.-A. (2009). Rheumatoid arthritis in UK primary care: Incidence and prior morbidity. *Scandinavian Journal of Rheumatology*, *38*(3), 173–177. https://doi.org/10.1080/03009740802448825

Roglic, G., & World Health Organization (Eds.). (2016). *Global report on diabetes*. World Health Organization.

Rosenberg, I. H. (1989). Summary comments. *The American Journal of Clinical Nutrition*, *50*(5), 1231–1233. https://doi.org/10.1093/ajcn/50.5.1231

Roubenoff, R. (2009). Rheumatoid cachexia: A complication of rheumatoid arthritis moves into the 21st century. *Arthritis Research & Therapy*, *11*(2), 108. https://doi.org/10.1186/ar2658

Roubenoff, R., Roubenoff, R. A., Ward, L. M., Holland, S. M., & Hellmann, D. B. (1992). Rheumatoid cachexia: Depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. *The Journal of Rheumatology*, *19*(10), 1505–1510.

Sahebari, M., Goshayeshi, L., Mirfeizi, Z., Rezaieyazdi, Z., Hatef, M. R., Ghayour-Mobarhan, M., Akhlaghi, S., Sahebkar, A., & Ferns, G. A. (2011). Investigation of the Association between Metabolic Syndrome and Disease Activity in Rheumatoid Arthritis. *The Scientific World Journal*, *11*, 1195–1205. https://doi.org/10.1100/tsw.2011.111

Saklayen, M. G. (2018). The Global Epidemic of the Metabolic Syndrome. *Current Hypertension Reports*, *20*(2), 12. https://doi.org/10.1007/s11906-018-0812-z

Šalamon, L., Morović-Vergles, J., Marasović-Krstulović, D., Kehler, T., Šakić, D., Badovinac, O., Vlak, T., Novak, S., Štiglić-Rogoznica, N., Hanih, M., Bedeković, D., Grazio, S., Kadojić, M., Milas-Ahić, J., Prus, V., Stamenković, D., Šošo, D., Anić, B., Babić-Naglić, Đ., & Gamulin, S. (2015). Differences in the prevalence and characteristics of metabolic syndrome in rheumatoid arthritis and osteoarthritis: A multicentric study. *Rheumatology International*. https://doi.org/10.1007/s00296-015-3307-0

Sandberg, M. E. C., Bengtsson, C., Källberg, H., Wesley, A., Klareskog, L., Alfredsson, L., & Saevarsdottir, S. (2014). Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *73*(11), 2029–2033. https://doi.org/10.1136/annrheumdis-2013-205094

Santo, R. C., Fernandes, K. Z., Lora, P. S., Filippin, L. I., & Xavier, R. M. (2018, October). *Prevalence of Rheumatoid Cachexia in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis*. Journal of Cachexia, Sarcopenia and Muscle. https://doi.org/10.1002/jcsm.12320

Shahin, D., Eltoraby, E., Mesbah, A., & Houssen, M. (2010). Insulin resistance in early untreated rheumatoid arthritis patients. *Clinical Biochemistry*, *43*(7–8), 661–665. https://doi.org/10.1016/j.clinbiochem.2010.01.012

Shepherd, J., Ng, B., Sommer, M., & Heymsfield, S. B. (2017). Body Composition by DXA. *Bone*, *104*, 101–105. https://doi.org/10.1016/j.bone.2017.06.010

Skeoch, S., & Bruce, I. N. (2015). Atherosclerosis in rheumatoid arthritis: Is it all about inflammation? *Nature Reviews. Rheumatology*. https://doi.org/10.1038/nrrheum.2015.40

Smolen, J. S., & Aletaha, D. (2015). Rheumatoid arthritis therapy reappraisal: Strategies, opportunities and challenges. *Nature Reviews Rheumatology*, *11*(5), 276–289. https://doi.org/10.1038/nrrheum.2015.8

Smolen, J. S., Breedveld, F. C., Burmester, G. R., Bykerk, V., Dougados, M., Emery, P., Kvien, T. K., Navarro-Compán, M. V., Oliver, S., Schoels, M., Scholte-Voshaar, M., Stamm, T., Stoffer, M., Takeuchi, T., Aletaha, D., Andreu, J. L., Aringer, M., Bergman, M., Betteridge, N., … van der Heijde, D. (2016). Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Annals of the Rheumatic Diseases*, *75*(1), 3–15. https://doi.org/10.1136/annrheumdis-2015-207524

Smolen, J. S., Landewé, R., Bijlsma, J., Burmester, G., Chatzidionysiou, K., Dougados, M., Nam, J., Ramiro, S., Voshaar, M., Vollenhoven, R. van, Aletaha, D., Aringer, M., Boers, M., Buckley, C. D., Buttgereit, F., Bykerk, V., Cardiel, M., Combe, B., Cutolo, M., … Heijde, D. van der. (2017). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Annals of the Rheumatic Diseases*, annrheumdis-2016-210715. https://doi.org/10.1136/annrheumdis-2016-210715

Sokka, T., Abelson, B., & Pincus, T. (2008). Mortality in rheumatoid arthritis: 2008 update. *Clinical and Experimental Rheumatology*, *26*(5 Suppl 51), S35-61.

Sokka T., T., Häkkinen, A., Kautiainen, H., Maillefert, J. F., Toloza, S., Mørk Hansen, T., Calvo-Alen, J., Oding, R., Liveborn, M., Huisman, M., Alten, R., Pohl, C., Cutolo, M., Immonen, K., Woolf, A., Murphy, E., Sheehy, C., Quirke, E., Celik, S., … QUEST-RA Group. (2008). Physical inactivity in patients with rheumatoid arthritis: Data from twenty-one countries in a cross-sectional, international study. *Arthritis and Rheumatism*, *59*(1), 42–50. https://doi.org/10.1002/art.23255

Solomon, D. H., Karlson, E. W., Rimm, E. B., Cannuscio, C. C., Mandl, L. A., Manson, J. E., Stampfer, M. J., & Curhan, G. C. (2003). Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation*, *107*(9), 1303–1307.

Srikanthan, P., Hevener, A. L., & Karlamangla, A. S. (2010). Sarcopenia Exacerbates Obesity-Associated Insulin Resistance and Dysglycemia: Findings from the National Health and Nutrition Examination Survey III. *PLOS ONE*, *5*(5), e10805. https://doi.org/10.1371/journal.pone.0010805

Srikanthan, P., & Karlamangla, A. S. (2011). Relative Muscle Mass Is Inversely Associated with Insulin Resistance and Prediabetes. Findings from The Third National Health and Nutrition Examination Survey. *The Journal of Clinical Endocrinology & Metabolism*, *96*(9), 2898–2903. https://doi.org/10.1210/jc.2011-0435

Stamp, L. K., James, M. J., & Cleland, L. G. (2005). Diet and Rheumatoid Arthritis: A Review of the Literature. *Seminars in Arthritis and Rheumatism*, *35*(2), 77–94. https://doi.org/10.1016/j.semarthrit.2005.05.001

St-Onge, M.-P., Janssen, I., & Heymsfield, S. B. (2004). Metabolic Syndrome in Normal-Weight Americans New definition of the metabolically obese, normal-weight individual. *Diabetes Care*, *27*(9), 2222–2228. https://doi.org/10.2337/diacare.27.9.2222

Summers, G. D., Metsios, G. S., Stavropoulos-Kalinoglou, A., & Kitas, G. D. (2010). Rheumatoid cachexia and cardiovascular disease. *Nature Reviews Rheumatology*, *6*(8), 445–451. https://doi.org/10.1038/nrrheum.2010.105

Symmons, D. P., Bankhead, C. R., Harrison, B. J., Brennan, P., Barrett, E. M., Scott, D. G., & Silman, A. J. (1997). Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: Results from a primary care-based incident case-control study in Norfolk, England. *Arthritis and Rheumatism*, *40*(11), 1955–1961. https://doi.org/10.1002/art.1780401106

The IPAQ group. (2003). *International Physical Activity Questionnaire.* ipaq.ki.se

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. (2002). *Circulation*, *106*(25), 3143–3143.

Timmis, A., Townsend, N., Gale, C. P., Torbica, A., Lettino, M., Petersen, S. E., Mossialos, E. A., Maggioni, A. P., Kazakiewicz, D., May, H. T., de Smedt, D., Flather, M., Zuhlke, L., Beltrame, J. F., Huculeci, R., Tavazzi, L., Hindricks, G., Bax, J., Casadei, B., … European Society of Cardiology. (2019). European Society of Cardiology: Cardiovascular Disease Statistics 2019. *European Heart Journal*. https://doi.org/10.1093/eurheartj/ehz859

Tournadre, A., Pereira, B., Dutheil, F., Giraud, C., Courteix, D., Sapin, V., Frayssac, T., Mathieu, S., Malochet-Guinamand, S., & Soubrier, M. (2017). Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. *Journal of Cachexia, Sarcopenia and Muscle*, n/a-n/a. https://doi.org/10.1002/jcsm.12189

Tournadre, A., Vial, G., Capel, F., Soubrier, M., & Boirie, Y. (2018). Sarcopenia. *Joint Bone Spine*. https://doi.org/10.1016/j.jbspin.2018.08.001

Tracy, A., Buckley, C. D., & Raza, K. (2017). Pre-symptomatic autoimmunity in rheumatoid arthritis: When does the disease start? *Seminars in Immunopathology*, *39*(4), 423–435. https://doi.org/10.1007/s00281-017-0620-6

Turesson, C., Bergström, U., Pikwer, M., Nilsson, J.-Å., & Jacobsson, L. T. H. (2016). A high body mass index is associated with reduced risk of rheumatoid arthritis in men, but not in women. *Rheumatology (Oxford, England)*, *55*(2), 307–314. https://doi.org/10.1093/rheumatology/kev313

Turk, S. A., van Schaardenburg, D., Boers, M., de Boer, S., Fokker, C., Lems, W. F., & Nurmohamed, M. T. (2018). An unfavorable body composition is common in early arthritis patients: A case control study. *PLoS ONE*, *13*(3). https://doi.org/10.1371/journal.pone.0193377

Uutela, T. I., Kautiainen, H. J., & Häkkinen, A. H. (2018). Decreasing muscle performance associated with increasing disease activity in patients with rheumatoid arthritis. *PloS One*, *13*(4), e0194917. https://doi.org/10.1371/journal.pone.0194917

Uyl, D. den, Raalte, D. H. van, Nurmohamed, M. T., Lems, W. F., Bijlsma, J. W. J., Hoes, J. N., Dijkmans, B. A. C., & Diamant, M. (2012). Metabolic effects of high-dose prednisolone treatment in early rheumatoid arthritis: Balance between diabetogenic

effects and inflammation reduction. *Arthritis & Rheumatism*, *64*(3), 639–646. https://doi.org/10.1002/art.33378

Van de Voorde, J., Pauwels, B., Boydens, C., & Decaluwé, K. (2013). Adipocytokines in relation to cardiovascular disease. *Metabolism*, *62*(11), 1513–1521. https://doi.org/10.1016/j.metabol.2013.06.004

van den Hoek, J., Roorda, L. D., Boshuizen, H. C., Tijhuis, G. J., Dekker, J., van den Bos, G. A., & Nurmohamed, M. T. (2016). Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: A prospective cohort study. *Clinical and Experimental Rheumatology*, *34*(5), 813–819.

van Gestel, A. M., Haagsma, C. J., & van Riel, P. L. (1998). Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis and Rheumatism*, *41*(10), 1845–1850. https://doi.org/10.1002/1529-0131(199810)41:10<1845::AID-ART17>3.0.CO;2-K

van Sijl, A. M., Peters, M. J., Knol, D. K., de Vet, H. C., Gonzalez-Gay, M. A., Smulders, Y. M., Dijkmans, B. A., & Nurmohamed, M. T. (2011). Carotid Intima Media Thickness in Rheumatoid Arthritis as Compared to Control Subjects: A Meta-Analysis. *Seminars in Arthritis and Rheumatism*, *40*(5), 389–397. https://doi.org/10.1016/j.semarthrit.2010.06.006

Verheggen, R. J. H. M., Maessen, M. F. H., Green, D. J., Hermus, A. R. M. M., Hopman, M. T. E., & Thijssen, D. H. T. (2016). A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: Distinct effects on body weight and visceral adipose tissue. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*, *17*(8), 664–690. https://doi.org/10.1111/obr.12406

Verhoeven, F., Tordi, N., Prati, C., Demougeot, C., Mougin, F., & Wendling, D. (2016). Physical activity in patients with rheumatoid arthritis. *Joint Bone Spine*, *83*(3), 265–270. https://doi.org/10.1016/j.jbspin.2015.10.002

Voigt, L. F., Koepsell, T. D., Nelson, J. L., Dugowson, C. E., & Daling, J. R. (1994). Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. *Epidemiology (Cambridge, Mass.)*, *5*(5), 525–532.

WHO. (1997). *World Health Organization. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation on obesity, 3-5 June 1997, WHO/NUT/NCD/98.1. WHO: Geneva, 1997*. https://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/

WHO. (2010). *Global recommendations on physical activity for health*. https://www.who.int/ncds/prevention/physical-activity/guidelines-global-recommendations-for-health/en/

WHO. (2020, March 3). *Obesity and overweight*. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Wilson, D., Jackson, T., Sapey, E., & Lord, J. M. (2017). Frailty and sarcopenia: The potential role of an aged immune system. *Ageing Research Reviews*, *36*, 1–10. https://doi.org/10.1016/j.arr.2017.01.006

Wolfe, F., & Michaud, K. (2012). Effect of body mass index on mortality and clinical status in rheumatoid arthritis. *Arthritis Care & Research*, *64*(10), 1471–1479. https://doi.org/10.1002/acr.21627

Yoshida, K., Lin, T.-C., Wei, M., Malspeis, S., Chu, S. H., Camargo, C. A., Raby, B. A., Choi, H. K., Tedeschi, S. K., Barbhaiya, M., Lu, B., Costenbader, K. H., Karlson, E. W., & Sparks, J. A. (2019). The roles of post-diagnosis accumulation of morbidities

and lifestyle changes on excess total and cause-specific mortality risk in rheumatoid arthritis. *Arthritis Care & Research*. https://doi.org/10.1002/acr.24120

Yu, Z., Yang, N., Everett, B. M., Frits, M., Iannaccone, C., Coblyn, J., Weinblatt, M., Shadick, N., Solomon, D. H., & Liao, K. P. (2018). Impact of Changes in Inflammation on Estimated Ten-Year Cardiovascular Risk in Rheumatoid Arthritis. *Arthritis & Rheumatology (Hoboken, N.J.)*, *70*(9), 1392–1398. https://doi.org/10.1002/art.40532

Zhang, J., Fu, L., Shi, J., Chen, X., Li, Y., Ma, B., & Zhang, Y. (2013). The risk of metabolic syndrome in patients with rheumatoid arthritis: A meta-analysis of observational studies. *PloS One*, *8*(10), e78151. https://doi.org/10.1371/journal.pone.0078151

14. PUBLICATIONS

15. CURRICULUM VITAE

Name: Raili Müller
Date of birth: 05.08.1981
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Address: University of Tartu, Institute of Clinical Medicine, L. Puusepa 8, 51014 Tartu, Estonia
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Education and professional employment

1988–1999	Tartu Kivilinna Gymnasium
1999–2005	University of Tartu, Faculty of Medicine, Medicine
2005–2011	University of Tartu, Faculty of Medicine, Residency in rheumatology
2012–2020	University of Tartu, Faculty of Medicine, PhD student
2010–...	Specialist, Institute of Clinical Medicine, Tartu University
2011–...	Rheumatologist, Department of Internal Medicine, Tartu University Hospital
2011–2015	Rheumatologist, Viljandi County Hospital
2015–...	Rheumatologist, OÜ Meditrials
2016–...	Assistant, Institute of Clinical Medicine, University of Tartu

Membership in scientific organizations:
Estonian Society for Rheumatology
Estonian Medical Association
Emerging EULAR NETwork

Scientific work
Research fields: rheumatoid arthritis, early arthritis, metabolic syndrome, insulin resistance, body composition

List of publications in international peer-reviewed journals:

Müller, R., Kull, M., Põlluste, K., Aart, A., Eglit, T., Lember, M., Kallikorm, R. (2017). The metabolic profile in early rheumatoid arthritis: a high prevalence of metabolic obesity. Rheumatol Int. 37(1):21–27.

Müller, R., Kull, M., Lember, M., Põlluste, K., Valner, A., Kallikorm, R. (2017). Insulin Resistance in Early Rheumatoid Arthritis Is Associated with Low Appendicular Lean Mass. BioMed research international, 2017, 9584720.

Müller, R., Kull, M., Põlluste, K., Valner, A., Lember, M., Kallikorm, R. (2019). Factors Associated With Low Lean Mass in Early Rheumatoid Arthritis: A Cross- Sectional Study. Medicina (Kaunas, Lithuania), 55(11), 730.

Starkopf, A., Müller, R., Starkopf, A., Aart, A., Kull, M., Põlluste, K., Lember, M., Kallikorm R. (2017). Physical function measures and health-related quality of life in primary care medicine: cross-sectional study. Family Medicine & Primary Care Review, 19(2), 161–166.

Põlluste, K., Aart, A., Kallikorm, R., Kull, M., Kärberg, K., Müller, R., Ots-Rosenberg, M., Tolk, A., Uhlinova, J., Lember, M. (2016). Adverse lifestyle and health-related quality of life: gender differences in patients with and without chronic conditions. Scand J Public Health. 44(2):209–16.

Müller, R., Kallikorm, R., Põlluste, K., Lember, M. (2012). Compliance with treatment of rheumatoid arthritis. Rheumatol Int. 32, 3131–3135

Khan, NA,. Yazici, Y., Calvo-Alen, J., Dadoniene, J., Gossec, L., Hansen, TM., Huisman, M., Kallikorm, R., Muller, R., Liveborn, M., Oding, R., Luchikhina, E., Naranjo, A., Rexhepi, S., Taylor, P., Tlustochowich, W., Tsirogianni, A., Sokka, T.; QUEST-RA Group (2009). Reevaluation of the role of duration of morning stiffness in the assessment of rheumatoid arthritis activity. The Journal of Rheumatology, 36 (11), 2435–2442.

Sokka, T., Häkkinen, A., Kautiainen, H., Maillefert, JF., Toloza, S., Mørk Hansen, T., Calvo-Alen, J., Oding, R., Liveborn, M., Huisman, M., Alten, R., Pohl, C., Cutolo, M., Müller, R., ..., Pincus, T.; QUEST-RA Group (2008). Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. Arthritis and Rheumatism, 15;59(1):42–50.

16. ELULOOKIRJELDUS

Nimi:	Raili Müller
Sünniaeg:	05.08.1981
Kodakondsus:	Eesti
Aaddress:	Tartu Ülikool, Kliinilise meditsiini instituut, L. Puusepa 8, 51014 Tartu, Eesti
E-mail:	raili.muller@kliinikum.ee

Haridus- ja ametikäik

1988–1999	Tartu Kivilinna Gümnaasium
1999–2005	Tartu Ülikool, Arstiteaduskond, Arstiteadus
2005–2011	Tartu Ülikool, Arstiteaduskond, Reumatoloogia residentuur
2012–2020	Tartu Ülikool, Meditsiiniteaduste valdkond, Kliinilise Meditsiini Instituut, doktoriõpe
2010–...	Spetsialist, Tartu Ülikool, Meditsiiniteaduste valdkond, Kliinilise Meditsiini Instituut
2011– ...	Reumatoloog, Tartu Ülikooli Kliinikumi Sisekliinik,
2011–2015	Reumatoloog, SA Viljandi haigla
2015–...	Reumatoloog, OÜ Meditrials
2016–...	Assistent, Tartu Ülikool, Meditsiiniteaduste valdkond, Kliinilise Meditsiini Instituut

Liikmelisus erialaseltsides
Eesti Reumatoloogia Selts
Eesti Arstide Liit
Emerging EULAR NETwork

Teadustöö suunad:
Reumatoidartriit, varane artriit, metaboolne sündroom, insuliiniresistentsus, keha koostis

Rahvusvahelistes eelretsenseeritud ajakirjades avaldatud artiklid:

Müller, R., Kull, M., Põlluste, K., Aart, A., Eglit, T., Lember, M., Kallikorm, R. (2017). The metabolic profile in early rheumatoid arthritis: a high prevalence of metabolic obesity. Rheumatol Int. 37(1):21–27.

Müller, R., Kull, M., Lember, M., Põlluste, K., Valner, A., Kallikorm, R. (2017). Insulin Resistance in Early Rheumatoid Arthritis Is Associated with Low Appendicular Lean Mass. BioMed research international, 2017, 9584720.

Müller, R., Kull, M., Põlluste, K., Valner, A., Lember, M., Kallikorm, R. (2019). Factors Associated With Low Lean Mass in Early Rheumatoid Arthritis: A Cross- Sectional Study. Medicina (Kaunas, Lithuania), 55(11), 730.

Starkopf, A., Müller, R., Starkopf, A., Aart, A., Kull, M., Põlluste, K., Lember, M., Kallikorm, R. (2017). Physical function measures and health-related quality of life in primary care medicine: cross-sectional study. Family Medicine & Primary Care Review, 19(2), 161–166.

Põlluste, K., Aart, A., Kallikorm, R., Kull, M., Kärberg, K., Müller, R., Ots-Rosenberg, M., Tolk, A., Uhlinova, J., Lember, M. (2016). Adverse lifestyle and health-related quality of life: gender differences in patients with and without chronic conditions. Scand J Public Health. 44(2):209–16.

Müller, R., Kallikorm, R., Põlluste, K., Lember, M. (2012). Compliance with treatment of rheumatoid arthritis. Rheumatol Int. 32, 3131–3135

Khan, NA., Yazici, Y., Calvo-Alen, J., Dadoniene, J., Gossec, L., Hansen, TM., Huisman, M., Kallikorm, R., Muller, R., Liveborn, M., Oding, R., Luchikhina, E., Naranjo, A., Rexhepi, S., Taylor, P., Tlustochowich, W., Tsirogianni, A., Sokka, T.; QUEST-RA Group (2009). Reevaluation of the role of duration of morning stiffness in the assessment of rheumatoid arthritis activity. The Journal of Rheumatology, 36 (11), 2435–2442.

Sokka, T., Häkkinen, A., Kautiainen, H., Maillefert, JF., Toloza, S., Mørk Hansen, T., Calvo-Alen, J., Oding, R., Liveborn, M., Huisman, M., Alten, R., Pohl, C., Cutolo, M., Müller, R., ..., Pincus, T.; QUEST-RA Group (2008). Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. Arthritis and Rheumatism, 15;59(1):42–50.

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95. **Mari Järvelaid**. Health damaging risk behaviours in adolescence. Tartu, 2004.
96. **Ülle Pechter**. Progression prevention strategies in chronic renal failure and hypertension. An experimental and clinical study. Tartu, 2004.
97. **Gunnar Tasa**. Polymorphic glutathione S-transferases – biology and role in modifying genetic susceptibility to senile cataract and primary open angle glaucoma. Tartu, 2004.
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