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ANNIKA VALNER

Changes in structure and function of extremities in early rheumatoid arthritis

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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications referred to in the text by their Roman numerals (I–III):

I Valner A, Kirsimägi Ü, Müller R, Kull M, Põlluste K, Lember M, Kallikorm R. Structural and Functional Changes of Hands and Legs in Early Rheumatoid Arthritis. *Medicina* (Kaunas). 2021;57(4):317.

II Valner A, Kirsimägi Ü, Müller R, Kull M, Põlluste K, Kumm J, Lember M, Kallikorm R. Factors associated with hand bone changes in early rheumatoid arthritis. *Musculoskeletal Care*. 2023;21(1):108–116.

III Valner A, Müller R, Kull M, Põlluste K, Lember M, Kallikorm R. Does dietary polyunsaturated fatty acid intake associate with bone mineral density and limb structural changes in early rheumatoid arthritis? *Nutrition and Metabolic Insights*. 2023;16:11786388231176169.

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ABBREVIATIONS

AA	arachidonic acid
ACR	American College of Rheumatology
Anti-CCP	anti-citrullinated protein antibodies
BMI	body mass index
BMC	bone mineral content
BMD	bone mineral density
CRP	C-reactive protein
Vitamin D3	vitamin D (cholecalciferol)
DAS28 score	disease activity score calculated using 28 joints
DMARDs	disease-modifying anti-rheumatic drugs
DXA	dual-Energy X-Ray Absorptiometry
ERA	early rheumatoid arthritis
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GCS	glucocorticoids
HST	Handgrip Strength Test
IFN-γ	interferon-gamma
IL-1β	interleukin-1 beta
IL-1	interleukin-1
IL-6	interleukin-6
IL-17	interleukin-17
MRI	magnetic resonance imaging
MTP joints	metatarsophalangeal joints
MTX	methotrexate
MyoD	myoblast determination protein
NSAIDs	nonsteroidal anti-inflammatory drugs
NF-κB	nuclear factor kappa B
OPG	osteoprotegerin
OS	oxidative stress
PTH	parathyroid hormone
PUFAs	polyunsaturated fatty acids
RA	rheumatoid arthritis
RANKL	receptor activator of nuclear factor kappa-B
RCTs	randomized controlled trials
RF	rheumatoid factor
RNS	reactive nitrogen species
ROS	reactive oxygen species
S	second, the SI unit of time
SHS	Sharp van der Heijde scoring
30-CST	Thirty-Second Chair Stand Test
TNF-α	tumour necrosis factor alpha
WHO	World Health Organization

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that mainly affects the small joints of the hands and feet (Scott et al., 2010). RA is characterized by immune cell infiltration and the hyperplasia of synovial fibroblasts, that leads to articular cartilage destruction, bone erosion (van der Woude et al., 2018; Xu et al., 2021; Patidar et al., 2022) and eventually irreversible loss of physical function (van Gestel et al., 1996; Andersson et al., 2021). Joint stiffness, pain, limitation of activity, and functional disability are direct results of inflammation (Niemantsverdriet et al., 2020).

RA is most common in women and elderly people. It influences 0.5–1.0% of adults. The prevalence of RA in Estonia among 20 years and older women was 0.70% (6.68–7.37) and men 0.16% (1.42, 1.79), (Otsa et al., 2013). RA is often accompanied with the presence of autoantibodies like rheumatoid factor (RF) and anti-citrullinated protein antibodies (anti-CCP). The main environmental risk factor of RA is smoking (Scott et al., 2010). Furthermore, it has been concluded that smoking is a risk factor for higher levels of RF and anti-CCP (Elzorkany et al., 2021). Anti-CCP positive RA is considered a more erosive RA subset compared to anti-CCP negative RA (van der Linden et al., 2009; Llorente et al., 2020). Genetic factors apply up to 50% of the risk of developing RA (Scott et al., 2010; Padyukov, 2022).

Bone structure changes of hand and leg joints can already be present in the early stage of arthritis (Boutry et al., 2003). In RA, osteoporosis (OP) has been considered as a frequent comorbidity (Wade et al., 2014; Llorente et al., 2020) and the prevalence of OP in RA is around 30 percent (Haugeberg et al., 2000; Hauser et al., 2014). A study of recent onset RA indicated that 18–20% of the joints of the hands and feet had radiographic joint damage after 3 years. Moreover, throughout the entire follow-up, more foot joints than hand joints were affected. It was also found that the damage in the foot joints appeared earlier than the damage in hand joints (van der Heijde et al., 1992).

Furthermore, RA can cause changes in body composition via decrease of hand and leg lean mass, and accumulation of fat mass in the trunk area (Book et al., 2009; Lemmey, 2016; Gabdulina et al., 2018; Turk et al., 2018; Efthymiou et al., 2022). In stable RA disease, considerable muscle loss can be detected in ~67% and obesity in ~80% of patients (Summers et al., 2008; Lemmey, 2016). Consequently, muscle weakness is often reported in RA patients, and even up to 70% reduction in muscular strength has been detected in patients with RA compared with age-matched healthy controls (Yamada et al., 2017). Muscle weakness reduces the quality of life (Book et al., 2009; Yamada et al., 2017), as well as increases the burden on society since patients' work ability lowers (Yamada et al., 2017).

Previous studies have shown that although treatments have become more effective and accessible, 70% of patients still experience RA disease specific bone structure changes in the first years of disease (van der Heijde et al., 1995). A total of 25% of patients already have them within three months of developing

RA (Nell et al., 2004). As RA is a systemic disease that can cause disability and affect quality of life, it is crucial to find out factors that associate with these arthritis-related changes. Combined hand and leg structural changes in early RA and the factors that associate with these changes have been so far rarely the focus of research. Our study was undertaken to discover if there are structural and functional changes of upper and lower limbs already present in early rheumatoid arthritis (ERA) and if the changes in hands and legs are similar. Hands and legs were evaluated in parallel as the structural and functional alterations of limbs have a great impact on everyday coping and can increase the burden on society via lowering of work ability (Yamada et al., 2017).

2. LITERATURE REVIEW

2.1. Early rheumatoid arthritis

The exact cause and the full pathogenesis of RA is still not completely known. A prolonged state of autoimmunity precedes the clinical start of RA. There are several phases in the development of RA: obtaining the genetic risk factors for the disease, followed by interactions between genes and environmental risk factors (such as smoking, respiratory mucosal inflammation, periodontitis, and alterations in intestinal microbiota). Environmental risk factors can activate an autoimmune reaction (Tracy et al., 2017) that may lead to clinical signs of RA.

Furthermore, current research reveals that oxidative stress (OS) also has a significant role in the pathogenesis of RA (Khojah et al., 2016; Bala et al., 2017; Zeng et al., 2021). The interaction between a body's exogenous and/or endogenous antigens and cellular immune system creates reactive nitrogen species (RNS) and reactive oxygen species (ROS). RNS and ROS activate the signalling cascades of inflammatory cells to synthesize pro-inflammatory cytokines and chemokines (Bala et al., 2017). RNS and ROS have definite parts in the destructive, proliferative synovitis of RA (Khojah et al., 2016). Moreover, in RA, OS distinctly contributes to the initiation and maintenance of systemic inflammation (Zeng et al., 2021).

It has been suggested that the treatment of RA should focus on early diagnosis that is followed by early initiation of disease-modifying anti-rheumatic drug (DMARD) therapy. Early rheumatoid arthritis has been considered as RA with less than one year of duration (Emery et al., 1997). The early phase of RA in within 3 months of the development of synovitis has been named the "window of opportunity" (Harnden et al., 2022). The timeframe is probably due to the knowledge that after the onset of the symptoms, the disease can progress rapidly, causing irreversible cartilage damage, sometimes in under 2 months. This damage can only be prevented by the early initiation of therapy. Additionally, patients in the earliest stages of RA respond better to treatment compared to patients with long-established disease (Barhamain et al., 2017). Ideally in ERA, the initiation of treatment in the first 3–6 months after symptom onset improves the possibility of achieving disease remission, reduces joint damage and disability (Demoruelle et al., 2012). Still, diagnosing and treating RA patients within this period can be complicated due to delays in symptom presentation, referral delays, and waiting times in secondary care (Barhamain et al., 2017; Harnden et al., 2022).

2.2. Structural and functional changes of hands and legs in rheumatoid arthritis

2.2.1. Bone structure changes

Bone structure changes are common in RA. Three types of bone loss can be identified: local – causing periarticular osteopenia; juxta-articular – associated with bone erosions; and systemic – generalized osteopenia and/or osteoporosis (Arboleya et al., 2013; Guo et al., 2018; Llorente et al., 2020). Local bone changes may be evident prior to the appearance of systemic changes.

Osteoporosis is a frequent systemic skeletal disorder defined by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and a susceptibility to fracture (Llorente et al., 2020). Osteoporosis may develop for several reasons, but in RA, periarticular osteoporosis or osteopenia are early characteristic signs of appendicular bone damage, preceding the development of erosions (Kilic et al., 2015). Hand bone loss may already occur in the early phase of RA (Daragon et al., 2001; Hill et al., 2010).

Local and generalized bone loss share the same pathway: the receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG) route (Takayanagi, 2009; Bultink et al., 2012), stimulating the activation, differentiation and proliferation of osteoclasts (Lacey et al., 1998; Bultink et al., 2012). In case there is an imbalance in bone remodelling, it can result in an increase in bone resorption, leading to reduction of bone mass, decrease in bone formation, and the inhibition of bone repair (Llorente et al., 2020). Bone loss is the result of the induction of osteoclasts and the suppression of osteoblasts (Guo et al., 2018). Osteoclasts are the essential cell population accounting for bone loss in RA patients, leading to bone erosions in RA (Gravallese et al., 1998; Guder et al., 2020; Llorente et al., 2020). Therefore, in RA, RANKL has a crucial role in the appearance of joint destruction (Bultink et al., 2012; Danks et al., 2016).

In addition to the aforementioned aspects, osteoprotegerin (OPG) has a regulatory role in bone remodelling via inhibiting osteoclastogenesis (Simonet et al., 1997). OPG may derive from body fat (Perez de Ciriza et al., 2014; Bianchi, 2018) and it is considered to prevent bone damage that may follow the synovial inflammation (Schett et al., 2003). The level of OPG lowers through osteoclastogenesis (Takayanagi et al., 2000; Llorente et al., 2020). Androgens reduce OPG levels, whereas estradiol has the opposite impact (Hofbauer et al., 2002; Bianchi, 2018). Bone loss may also be induced by immobilization (Pathak et al., 2015) and physical inactivity (Prioreschi et al., 2015; Fenton et al., 2018). Mechanical loading of bone may prevent osteoclast-related bone loss in RA (Pathak et al., 2015).

Therefore, considering that bone loss may already appear in the early stage of RA (Daragon et al., 2001; Hill et al., 2010), it is important to identify different bone changes as early as possible. In RA, the Larsen score is usually used for evaluating RA related radiographic joint damage (erosions, joint space narrowing, bony outlines) on hand and leg radiographs (Larsen et al., 1977). Still, periarticular osteoporosis cannot be quantified based on the visual impression seen on the radiographs and must be detected via quantitative bone mass measures (Hoff et al., 2010). Dual Energy X-ray Absorptiometry (DXA) is a commonly used cheap and sensitive method to assess bone mass, bone mineral density (BMD) and bone mineral content (BMC), (Kilic et al., 2015; Sangondimath et al., 2023). Bone mass is a composite measure of bone size and mineral density, being a determinant of bone strength acquired during skeletal growth and development (DiMeglio et al., 2013). BMC is regarded as the total amount of mineral content of bone tissue in the whole skeleton or in a specific region, and it is measured in grams. BMD values are created by dividing the BMC (grams) by the bone area (cm^2), where it was measured (Clasey et al., 1997). In ERA, DXA can be a more sensitive tool than radiology (radiographic joint-damage scores), for evaluating arthritis-related bone damage (Haugeberg et al., 2007) or functional status (Njeh et al., 2000; Haugeberg et al., 2006; Kilic et al., 2015).

In view of the mentioned methods, a study of early RA patients indicated that bone mineral density in lumbar and femoral neck regions, as well as total bone mineral density in RA patients were significantly lower compared with age-matched controls (Sahin et al., 2006). Bone loss in early RA occurred more quickly in the hand, than in the hip and spine (Haugeberg et al., 2007). Bone damage associated with the level of synovitis and was not present in the absence of joint inflammation (Conaghan et al., 2003; Haugeberg et al., 2006). Additionally, in women, reduced BMD at the lumbar spine or hip at the onset of RA was associated with a higher Larsen score at baseline and also after 2 years of disease clinical start, suggesting that the reduction of bone mass and joint destruction in RA may have a common pathophysiological mechanism (Forslind et al., 2003).

The presence of bone erosions has been recognized as a hallmark of RA, caused by the inflammatory process and resulting in various degrees of joint destruction and disability. At the diagnosis of RA, the distribution of erosions may differ and are most frequently detected in the hands and/or feet. Therefore, the methods for scoring erosions are based on conventional radiographs of hands and feet, usually evaluated by the Sharp van der Heijde scoring (SHS) method (assessing erosive changes and joint space narrowing in 32 joints in the hands and 12 joints in the feet), (van der Heijde, 2000; Andersson et al., 2021).

Previous research indicated that in early RA, similar amount of bone erosions were found in the metacarpophalangeal joints and in the metatarsophalangeal (MTP) joints. This finding suggests that additional imaging of feet may be beneficial when assessment of hands do not confirm the diagnosis of RA (Boutry et al., 2003). Even though it is not yet a common procedure in everyday clinical practice, the assessment of hand and leg bone mass in parallel could help to prognose the course of disease for early arthritis (Llorente et al., 2020). Therefore, bone mass change evaluation of upper and lower limbs in ERA could be advantageous for an earlier diagnosis and start of treatment.

2.2.2. Muscle and fat structure changes

Altered body composition is a common finding in RA. In established RA, up to two thirds of patients have a phenotype characterized by muscle wasting (Challal et al., 2016) and an increase of fat mass without body weight variations (Ferguson et al., 2019; Gioia et al., 2020). This is mainly identified by loss of appendicular lean mass and accumulation of fat mass in the trunk area (Book et al., 2009; Lemmey, 2016; Gabdulina et al., 2018; Turk et al., 2018; Efthymiou et al., 2022). In stable RA patients, significant muscle loss is usually found in ~67% and obesity in ~80% of cases (Summers et al., 2008; Lemmey, 2016). Lean mass of arms and legs can already be lowered in early RA (Book et al., 2009).

Decrease of lean mass seems to be the result of various mechanisms, including an excessive production of inflammatory cytokines and increased protein degradation (Roubenoff et al., 1994; Walsmith et al., 2004; Efthymiou et al., 2022). Still, the data about the involved factors are currently inconclusive and the changes in body composition could not solely be explained by the usual markers for RA disease severity and disease activity (Book et al., 2009).

The presence of low physical activity levels and a sedentary lifestyle may result in an increased accumulation of fat mass (Tierney et al., 2012; Santillán-Díaz et al., 2018; Efthymiou et al., 2022) additionally inducing inflammation (Fenton et al., 2018). In RA, pain, fatigue and joint stiffness further reduce physical activity (Hall et al., 2004; Turk et al., 2018), also causing lean mass lowering and a weight increase. Obesity alone is a risk factor for the development of arthritis in general (Unriza-Puin et al., 2017; Turk et al., 2018). It was found that subjects with body mass index (BMI) ≥ 30 had nearly threefold increased risk to have inflammatory arthritis (Lahiri et al., 2014). In contrast, other research has indicated that RA patients with low or normal BMI had radiographically more evident progression after 3 years, than RA patients with high BMI (Westhoff et al., 2007; Book et al., 2009).

The RA-related accelerated lean mass loss itself contributes to the loss of physical function and quality of life too. It is also probably associated with a decreased level of exercise due to sarcopenia (Book et al., 2009). Sarcopenia is defined as low muscle strength and low muscle mass (Moschou et al., 2023). A decrease in lean mass could possibly have several unfavourable consequences, including increased risk for joint destruction, disability, in addition to an elevated risk for falls and fractures (Book et al., 2009). In ERA patients, hand grip strength was significantly lower in RA patients compared with controls (Sahin et al., 2006). Furthermore, muscle strength had a major part in preventing arthritic bone loss (Liphardt et al., 2020).

A cross-sectional study of RA patients indicated that most of the subjects were physically inactive with no regular weekly exercise. Furthermore, physical inactivity was associated with female gender, older age, lower education, obesity, comorbidity, low functional capacity, and higher levels of disease activity, pain, and fatigue (Sokka et al., 2008).

Measuring lean and fat mass is clinically important because loss of lean mass in the limbs may cause weakness and disability (Baumgartner et al., 2004; Janssen, 2006; Book et al., 2009). Several studies show that exercise improves muscle function without affecting disease activity. Moreover, research evaluating radiographic joint damage as an endpoint also finds no evidence that even high-intensity exercise increases inflammation or joint damage (Plasqui, 2008). Therefore, it is important that RA patients are physically active (Santillán-Díaz et al., 2018).

Body composition, especially the amount of fat and lean mass located in the arms and legs, is strongly associated with disability in RA patients (Giles et al., 2008). In ERA, upper limbs structural changes occurred earlier than in lower limbs (Haugeberg et al., 2007). Although RA is a systemic disease, in ERA the structural changes in hands and legs may possibly not occur in parallel. Arthritis involvement may be different among patients, indicating the relevance in ERA to assess both hands and legs concurrently and separately in order to have a better overview of the RA disease course in the early stage.

2.2.3. Hand and leg changes in general

RA is a systemic disease mostly affecting the hand and leg joints (Scott et al., 2010), ultimately resulting in activity impairment and functional disability (Niemantsverdriet et al., 2020).

In RA, commonly only the small joints of hands are assessed while evaluating disease activity, as most widely used scales do not assess the small joints of legs. Joint destruction in RA is commonly evaluated by radiographs of both hands and feet (SHS method), whilst the inflammatory activity is mainly evaluated by a disease activity score calculated using 28 joints (DAS28 score) which, however, does not include the feet (Andersson et al., 2021).

At the same time, in early RA patients, involvement of foot joints is frequent (Michelson et al., 1994; Stolt et al., 2017; Andersson et al., 2021), being present in >50% of patients at any time after diagnosis of RA (Michelson et al., 1994). Furthermore, up to 50% of RA patients have some kind of foot problems already at diagnosis (Bálint et al., 2003; Andersson et al., 2021). In RA, destruction of the foot joints often precedes the development of destruction of other joints (Terao et al., 2015). It has been evaluated that continuing foot involvement in patients with longstanding RA is 30–90% (Michelson et al., 1994; Otter et al., 2010; van der Leeden et al., 2010; Andersson et al., 2021). The metatarsophalangeal joints are usually the first anatomical location on the foot where symptoms appear (van der Leeden et al., 2006; Andersson et al., 2021). Additionally, foot pain was the prevalent symptom in a third of cases (Otter et al., 2010; Stolt et al., 2017) affecting everyday life and coping (Williams et al., 2012; Stolt et al., 2017). Forefoot joint damage in RA is associated with increased pressure under the forefoot, particularly due to pressure under the first and fourth MTP joints (van der Leeden et al., 2006).

In a study of ERA patients, it was found that 77% of subjects had erosions in MTP joints (Boutry et al., 2003) and erosive changes were equally evident both in hand and leg joints (Boutry et al., 2003; Calisir et al., 2007). A prospective follow-up study of recent onset RA showed that up to 20% of hand and feet joints had radiographic RA-related joint damage after 3 years. During the whole follow-up, foot joints were even more affected than the hand joints. In addition, the destruction in the foot joints emerged earlier than the damage in hand joints (van der Heijde et al., 1992). Still contrastingly, another study indicated, that in ERA hand joint changes were more evident than leg joint changes (Dakkak et al., 2020).

In ERA patients with normal magnetic resonance imaging (MRI) scans of finger joints, additional MRI scans of the forefeet revealed synovitis and bone oedema (Ostendorf et al., 2004). Foot joint destruction may have different causes than the damage in hand joint (Terao et al., 2015). Imaging of the legs in ERA adds an extra tool which can potentially allow an earlier and more accurate diagnosis, and thus start treatment sooner (Ostendorf et al., 2004). According to previous research, both hands and legs can be affected in ERA, although reported data about appearing changes vary. Therefore, a supplementary study of apart evaluation of hands and legs in ERA is needed to identify the parallel emerging structural and functional changes of upper and lower extremities in ERA. The results of the study could be important in future assessment of disease activity, possibly indicating the need to include the evaluation of leg joints in the disease activity assessment scales.

2.3. Inflammatory markers in rheumatoid arthritis

In RA, the inflammation in the synovium induces the production of many cytokines (interleukin (IL)-1, (IL-6), and tumour necrosis factor alpha (TNF-α), (Abdel Meguid et al., 2013; Fardellone et al., 2020). TNF-α, IL-1, IL-6 and IL-17 upregulate RANKL and via it ultimately trigger osteoclastogenesis (Schett et al., 2010; Geusens et al., 2011; Bultink et al., 2012), and mediate cartilage and bone destruction of the joints. Subsequently, the inflammatory reaction may result in generalized bone loss. In RA, high levels of TNF-α have been found in parallel both in synovial fluid and in serum (Bulina et al., 2010). IL-6 has an important role in inflammation, and a direct effect on general, as well as on local bone loss in RA (Abdel Meguid et al., 2013; Fardellone et al., 2020).

TNF-α and interleukin-1 beta (IL-1β) also have a powerful influence on whole-body protein and energy metabolism (Rall et al., 2004). Research has shown that skeletal muscle protein loss depends on the combined signalling activities of TNF-α, interferon-gamma (IFN-γ), and the activity of nuclear factor kappa B (NF-κB) is needed for these cytokines to cause muscle damage. TNF-induced activation of NF-κB has been especially found to inhibit skeletal muscle differentiation via suppressing myoblast determination protein (MyoD). MyoD regulates the differentiation of skeletal muscle and is therefore crucial for the repair of damaged tissue (Guttridge et al., 2000; Rall et al., 2004). TNF-α acts synergistically with IL-1β, and via expression of IL-1, is associated with accelerated muscle loss (Moschou et al., 2023).

Moreover, IL-6 increases muscle metabolism with subsequent muscle wasting (Rall et al., 2004; Turk et al., 2018). High levels of IL-6 lowers mobility and is associated with loss of muscle strength (Moschou et al., 2023).

Previous research of early arthritis patients found that a higher ESR value was associated with higher fat mass, mostly distributed in the trunk in cases of longer symptom presence. Still, there was no association between disease activity, acute phase proteins and muscle mass changes (Turk et al., 2018).

CRP has a direct role in the activation and alteration of osteoclast differentiation in RA, which may lead to bone destruction (Ciurtin et al., 2024). CRP is also a relevant element for the RA DAS28-CRP disease activity score (Anderson et al., 2012) and therefore is a commonly used RA marker. Even though a great number of studies have shown a good correlation between CRP levels and disease activity in RA, using CRP as a marker of active disease raises various concerns. A subgroup of RA patients has been identified which lacks elevated CRP levels, even during severe flare-ups. As a result, the diagnosis and initiation of DMARD therapy may be significantly delayed compared to patients with increased CRP during flare-ups (Ciurtin et al., 2024).

Different inflammatory markers may cause differing structural and functional changes (Rall et al., 2004; Abdel Meguid et al., 2013; Turk et al., 2018; Fardellone et al., 2020; Moschou et al., 2023; Ciurtin et al., 2024). Therefore, it is relevant to analyse various inflammatory markers that may have a role in the appearance of RA-related limb structural changes in the early phase of the disease. Furthermore, as RA predominantly damages the hand and leg joints, it is necessary to separately evaluate the hand and leg changes due to the rise in inflammatory markers, as the changes may differ. Data on this topic remain sparse.

2.4. Hand bone mineral density and appearance of arthritis related erosions in early rheumatoid arthritis

RA has classically been identified by the presence of erosions (van der Woude et al., 2018; Xu et al., 2021). Erosion mainly affects intra-articular cortical bone and is a result of unpaired bone resorption and formation (Rossini et al., 2017). In RA, small joints (Guo et al., 2018), and hand joints are affected. A recent study found that the prevalence of erosions was significantly lower in seronegative (RF and anti-CCP negative) ERA patients, and in patients without elevated acute phase reactants. Furthermore, even longer disease duration was not related to a different prevalence of erosions in seronegative RA (Ulijn et al., 2023).

DXA assessment of the whole hand is more feasible and has better precision compared with local measures around single joints. Hand DXA also reflects the whole inflammatory reaction occurring in all affected joints of the hands (Alenfeld et al., 2000; Haugeberg et al., 2007).

Previous research has indicated that hand BMD lowering during the first three months of ERA could independently predict radiographic joint damage after one year of disease anamnesis (Ziegelasch et al., 2017). Periarticular BMD loss may already be present at the clinical manifestation of ERA (Iwata et al., 2016) and hand BMD lowering appears prior to generalized bone loss (Fardellone et al., 2020). Furthermore, periarticular osteoporosis/osteopenia appear before the development of erosions (Black et al., 2014; Kilic et al., 2015). A recent study found that bone erosions occurrence was related to systemic bone loss since the earliest phases of RA (Bruno et al., 2021). Hand BMD lowering in conjunction with age, was associated with increased predisposition to erosive disease. BMD lowering assessment in ERA may be beneficial to determine the risk of the appearance of erosions of initially non-erosive arthritis patients (Black et al., 2014). Osteoporosis itself might be a relevant and independent determinant of bone erosions in RA, but it needs further investigation (Rossini et al., 2017).

Contemporary information about factors associated with hand bone mass and BMD changes in ERA are insufficient (Black et al., 2014; Kilic et al., 2015; Rossini et al., 2017) and we could not find data about leg bone BMD changes associated with the appearance of RA related erosions. Considering that erosions are the destructive element in RA (Guo et al., 2018), and local bone changes in ERA could precede systemic changes, additional research is required.

2.5. Markers related to hand bone mineral density decrease and erosive changes in early rheumatoid arthritis

A decrease in hand BMD may be the initial change triggered by ERA, due to inflammation (Black et al., 2014). Vitamin D is crucial for BMD due to its essential role in calcium metabolism. Vitamin D deficiency can cause osteoporosis, and its supplementation is known to have a positive effect on BMD (Tomizawa et al., 2019; Kwon et al., 2020). Recent research indicates that administration of vitamin D supplementation may lower levels of RANKL and associated cytokines, and via it potentially lower inflammation (Ilchovska et al., 2021).

Several studies have evaluated the clinical significance of serum concentration of OPG, and it has been found that low serum OPG is associated with prevalent vertebral fracture in osteoporotic patients (Fahrleitner-Pammer et al., 2003; Chi et al., 2023). Contrastingly, another study indicated that an increase in serum OPG correlated negatively with BMD (Ostrowska et al., 2015; Chi et al., 2023). Moreover, OPG was found to be significantly higher in RA subjects compared with controls, correlating with inflammatory activity (Asanuma et al., 2007; Soliman et al., 2024). A recent meta-analysis indicated that the DAS28 disease activity score was positively associated with OPG levels in RA patients. Also, in ERA higher OPG levels was influenced by race, disease duration, and BMI (Wang et al., 2017). Therefore, OPG may potentially be a sensitive method for detection of active bone and cartilage destruction in RA (Karsdal et al., 2011; Soliman et al., 2024).

RF positive male RA patients have been found to have an elevated risk of fragility fractures (Filho et al., 2014), although not all researchers have verified the association between BMD loss and RF positivity (Amkreutz et al., 2021). Moreover, in ERA, anti-CCP positivity was associated with significantly lower BMD at the time of diagnosis, but not with greater BMD loss over the years after receiving treatment (Amkreutz et al., 2021).

Anti-CCP positive RA is considered a more erosive arthritis subset (van der Linden et al., 2009; Llorente et al., 2020). Furthermore, anti-CCP and RF positivity were discovered to predict progression of erosive changes in 5 years' time in ERA (Rydell et al., 2021). RF positivity was also associated with foot joint destruction (Terao et al., 2015). Also, a recent study found that high BMI is associated with less erosive changes in patients with anti-CCP positive RA (van der Helm-van Mil et al., 2008). In ERA, the distribution of body fat may have an impact on cartilage damage in ERA due to hormonal factors (Rydell et al., 2021).

As hand BMD lowering can be an early sign of ERA (Black et al., 2014), and the presence of bone erosions can result in joint damage and disability (Andersson et al., 2021), it is crucial to find out the factors that relate to hand BMD and erosive changes, and if the factors that associate with these specific changes are different from each other.

2.6. Dietary and smoking habits in early rheumatoid arthritis

2.6.1. Dietary habits

A healthy diet is fundamental for preventing various chronic conditions and adverse health effects (including obesity and OP) according to World Health Organization (WHO) data (WHO, 2019; WHO, 2024). In RA, dietary habits may increase the risk of disease manifestation and be a preventive factor (Raslan et al., 2024). Several randomized controlled trials (RCTs) have been published which involve the use of fatty acids with antioxidative effects (Richard et al., 2008) in the treatment of RA patients, although the outcome and interventions of these RCTs vary (Zeng et al., 2021). Moreover, among conducted research, some studies have evaluated the relationship between dietary consumption of polyunsaturated fatty acids (PUFAs) and RA. PUFAs have an important influence on immune system and inflammatory diseases. Omega-6 PUFAs have mostly proinflammatory effects, while omega-3 PUFAs exert anti-inflammatory and proresolving features (Navarini et al., 2017). Omega-3 PUFAs, which are mostly found in fish oils, present inverse correlations with CRP and IL-6 levels (Gioia et al., 2020). In RA, supplementation of omega-3 PUFA has been found to diminish pain, morning stiffness, and the frequency of NSAID consumption (Navarini et al., 2017; Skoczyńska et al., 2018), and has also been associated with lower disease-activity-related markers (Gioxari et al., 2018; Philippou et al., 2021;

Sigaux et al., 2022). In France, PUFA supplementation is already an official recommendation for RA patients for symptomatic relief (Daien et al., 2022).

Vegetable oils and animal sources are the main dietary sources of omega-6 PUFAs (Navarini et al., 2017). Higher omega-6 fatty acid intake in RA has been associated with increased serum levels of IL-6 and CRP (Sundrarjun et al., 2004; Lourdudoss et al., 2018). PUFA omega-6 arachidonic acid (AA) type inhibits osteoblastogenesis (Navarini et al., 2017), changes the osteoblast differentiation process and advances bone mass loss (Casado-Díaz et al., 2013; Navarini et al., 2017). Hence, a higher ratio of omega-3/omega-6 fatty acid in diet is considered a protective element against BMD lowering (Albertazzi et al., 2002; Navarini et al., 2017), and early manifestations of RA could potentially be delayed via the dietary intake of PUFAs (Gioia et al., 2020). Therefore, dietary consumption of PUFAs could be advantageous for the prevention of RA-caused BMD decreases.

Most established RA patients have a phenotype described by muscle wasting and an increase of fat mass without body weight changes (Ferguson et al., 2019; Gioia et al., 2020). There have been numerous studies evaluating the possible health benefits of omega-3 fatty acids, with data indicating its positive effects in sustaining muscle mass (Cena et al., 2020). Omega-3 long chain PUFA supplementation positive effect on overall body muscle mass and strength has been confirmed by several meta-analyses (Bird et al., 2021; Ma et al., 2021). For that reason, dietary consuming of PUFAs could be beneficial in avoidance of RA-associated structural changes of limbs.

Dietary habits may lead to overweight and obesity (Liu et al., 2013; Fu et al., 2021). A high omega-6 to omega-3 FA ratio especially increases obesity risk (Simopoulos, 2016; Lourdudoss et al., 2018). Obese patients have impaired intestinal immunity, which can be lessened by omega-3 PUFAs supplementation (Tilg, 2010; Fu et al., 2021). Additionally, omega-3 PUFAs may prevent the appearance of obesity by modulating gut microbiota and influencing the function of white adipose tissue (Kalupahana et al., 2020). Metabolic syndrome itself is an important risk factor in the development of arthritis (Lahiri et al., 2014).

Furthermore, RA is frequently associated with reduced muscle mass, which reflects an imbalance between protein synthesis and protein breakdown (Mikkelsen et al., 2015). Previous research has shown that low dietary protein intake was related to quicker lowering of muscle strength in older persons with a pro-inflammatory state (Bartali et al., 2012) and with decreased appendicular lean mass in ERA (Müller et al., 2019). Additionally, several studies have demonstrated a relationship between low protein intake and loss of muscle mass/strength (McLean et al., 2016; Torii et al., 2023). Furthermore, a recent study indicated that the rate of muscle protein synthesis and muscle gene expression can be stimulated via protein intake alone, and in combination with physical exercise in patients with well-treated RA, to a similar extent as in healthy individuals. The finding suggests that RA patients with moderate inflammation have maintained their muscle anabolic responsiveness to physical activity and protein intake (Mikkelsen et al., 2015). Therefore, in addition to exercise therapies, appropriate nutritional intake is one of the principal strategies to increase muscle mass and strength (Fiatarone et al., 1994; Torii et al., 2023). Moreover, dietary protein supplementation has indicated an increase in both muscle strength and physical performance (Tieland et al., 2012; Torii et al., 2023). Multiple consensus statements recommend an average protein intake of at least 1–1.5 g/kg/day (Bauer et al., 2013, 2019; Torii et al., 2023) and in cases of severe disease and inflammation, up to the upper limit of 2 g/kg/day (Bauer et al., 2019; Torii et al., 2023). Still, excessive consumption of protein has been linked to an elevated risk of inflammatory polyarthritis (Raslan et al., 2024).

A recent study indicated that in RA patients, higher adherence to the Mediterranean diet was related to lower disease activity and impact, and lower functional disability (Charneca et al., 2023). On the contrary, another study did not find an association between the Mediterranean diet score and the disease activity of people with rheumatoid arthritis (Mostafaei et al., 2024).

A meta-analysis including over 200,000 subjects indicated that high vitamin D intake lowered the risk of developing RA by 24% (Song et al., 2012; Maisha et al., 2023). A number of studies have suggested vitamin D supplementation aiding patients with established RA (Guan et al., 2020; Maisha et al., 2023).

Diet significantly influences intestinal microbiota, which in turn plays an important role in the development of RA (Raslan et al., 2024). Several studies have suggested that the intake of probiotics may be advantageous in reducing the risk of developing arthritis or reducing the arthritic process (Liu et al., 2016; Jubair et al., 2018; Gunes-Bayir et al., 2023). A Swedish cross-sectional study found that the RA patients had higher saturated fat consumption; lower carbohydrate energy and fibre intakes; and lower intakes of several micronutrients (vitamin A and D, folate, and calcium) (Turesson et al., 2022). Furthermore, excessive intake of red meat has been linked to an elevated risk of inflammatory polyarthritis. This may be due to increased inflammation caused by meat fats and nitrites and increased synovial involvement due to an excessive oral iron load (Raslan et al., 2024). High sodium intake is associated with increased risk of RA (Salgado et al., 2015).

Daily consumption of sugar-sweetened soda increases the risk of RA. High-fructose-flavoured soft drinks may help boost arthritis development in young adults by producing an excessive buildup of glycation products, enhancing inflammation (DeChristopher et al., 2016; Raslan et al., 2024). Consuming four or more cups of decaffeinated coffee per day is associated with elevated risk of having seropositive RA. Still, people who drank more than three cups of tea daily had a lower risk of seropositive RA (Mikuls et al., 2002).

Any level of alcohol consumption, both acute and chronic, has immunomodulatory effects. Heavy or moderate alcohol consumption can influence gut barrier integrity and the microbiome, and thus possibly contribute to RA (Azizov et al., 2021).

Taking everything into consideration, dietary habits can possibly have an influence on body structural changes in RA, especially PUFAs due to their anti-oxidative effects. Still, additional research is needed to evaluate the association between dietary habits and separate evaluation of hand and leg structural and functional changes in ERA, as data about early arthritis are lacking.

2.6.2. Smoking habits

Smoking is a risk factor for RA, contributing up to 25% of population-attributable risk of RA (Costenbader et al., 2006; Källberg et al., 2011; Lahiri et al., 2014) and higher pack-years are associated with an increased risk of RA (Costenbader et al., 2006). The correlation between smoking and the risk of anti-CCP negative RA disappeared entirely twenty years after stopping. Contrastingly, the correlation with the risk of anti-CCP positive RA remained linked to the number of cigarettes smoked (Shekhar et al., 2023).

Smoking is associated with osteoporosis through disruption of bone remodelling mechanisms via the RANKL-RANK-OPG pathway (Al-Bashaireh et al., 2018; Radmilović et al., 2023) and smokers were found to have significantly lower levels of OPG (Al-Bashaireh et al., 2018). Smoking is considered to suppress parathyroid hormone (PTH), (Al-Bashaireh et al., 2018) and reduce bone mass via its impact on vitamin D and calcium impaired absorption (Krall et al., 1991, 1999; Rapuri et al., 2000; Cusano, 2015; Al-Bashaireh et al., 2018). Furthermore, smoking is a known risk factor for lower BMD in the general population and RA patients (Llorente et al., 2020). It is also a risk factor for the progression of erosions (van der Linden et al., 2009; Llorente et al., 2020; Elzorkany et al., 2021). Tobacco smokers generally have lower body weight and BMI compared to non-smokers, as nicotine decreases appetite (Mineur et al., 2011; Al-Bashaireh et al., 2018).

Dietary and smoking habits can cause different body structure changes (van der Linden et al., 2009; Müller et al., 2019; Gioia et al., 2020; Llorente et al., 2020; Bird et al., 2021; Elzorkany et al., 2021; Ma et al., 2021). Therefore in ERA, separate hand and leg structure assessment, along with evaluation of nutritional and smoking status, could be additionally advantageous in RA patient disease progression assessment.

2.7. Summary of the literature review

Rheumatoid arthritis is a chronic inflammatory autoimmune disease primarily affecting the small joints of the hands and feet, causing synovitis, bone erosions, and muscle and fat structure changes. The pathophysiological mechanisms causing the structural and functional changes in the ERA remain less than fully understood. In RA, the structural and functional changes of the body can cause significant impairment of a patient's quality of life.

Despite RA's systemic nature, in early stage of the disease the structural and functional changes in hands and legs may possibly not appear in parallel, and there are no studies comparing the first changes in limbs. Moreover, changes may be present far before the onset of clinical manifestation of the disease and patients seeking the care of a rheumatologist. It has been shown that early diagnosis and treatment of rheumatoid arthritis improves health outcomes. However, there are no good generally accepted early markers for prognosing the course of early arthritis. Markers associated with body structure changes in ERA are of great interest in better understanding the reasons for the progression of the disease. DXA is frequently used to separately measure BMD and arm and leg bone, lean, and fat mass. Determining early changes in limb structure and function may be a new way to prognosing the disease course and activity. A decrease in hand BMD during the first months of the manifestation of RA could be a predictor of RA related joint damage in the early stage of the disease. Data about leg structural and functional changes in ERA are lacking. Furthermore, most commonly used scales do not even evaluate leg joints while assessing arthritic disease activity.

Several studies have tried to explore the lifestyle related factors in rheumatoid arthritis. Dietary and smoking habits have been studied extensively as they can have an impact on body structural changes. But in ERA, results remain inconclusive. Therefore, research of the separate evaluation of hands and legs structural and functional changes, as well as the markers that might be related to these alterations, is needed.

3. AIMS OF THE THESIS:

The general aim of this study was to evaluate the presence of structural and functional changes of hands and legs in early rheumatoid arthritis as well as factors related to the changes.

Specific aims were:

1. to assess if there are structural and functional changes of hands and legs already present in early rheumatoid arthritis and if the changes in hands and legs are similar (Paper I, II);
2. to examine the associations between hand and leg structural and functional changes with inflammatory markers (Paper I, II, III);
3. to assess if hand bone mineral density is related to the appearance of arthritis associated erosions (Paper II);
4. to find clinical lifestyle markers that are related to hand bone mineral density lowering and erosive changes in early rheumatoid arthritis (Paper II);
5. to identify if hand and leg structural changes in early rheumatoid arthritis associate with dietary and smoking habits (Paper I, II, III).

4. SUBJECTS AND METHODS:

4.1. Subjects

4.1.1. Early rheumatoid arthritis group (Papers I–III)

The thesis is based on a cross-sectional study of 83 patients with ERA, aged 19–79 years. To form the study group, 100 consecutive patients referred to Tartu University Hospital with newly diagnosed RA were recruited between January 2012 and May 2014. Their diagnoses were established according to American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2012 criteria for RA (Aletaha et al., 2010). RA patients with symptom duration up to one year (early arthritis) were invited to participate in the study. Nine patients with missing outcome data were excluded, as were another 8 patients who did not fulfil ACR/EULAR 2012 criteria for RA on a follow-up visit one year after their first visit (n=83).

4.1.2. Population-based comparison group (Papers I–III)

350 subjects adjusted for the age and gender composition of the Estonian population in 2013 were randomly selected from a primary healthcare centre practice list (the total number of subjects was 1854). Cross-sectional data were assembled from September 2014 to March 2015. Invitations containing introductory materials were sent to 350 people. The primary healthcare centre was contacted by 332 subjects seeking further instructions, and 330 people were ultimately recruited to the study. Six patients with missing outcome data were excluded and three subjects missed their study appointment (n=321).

All study participants signed written informed consent forms. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee of the University of Tartu (early rheumatoid arthritis group study approval: 221/M-9, date of approval 17 December 2012), population group study approval number 238/M-15 (date of approval 16 July 2014).

4.2. Methods

4.2.1. Medical interview

At first a face-to-face medical interview was done to gather information on the onset of arthritis, specifically the appearance of joint swelling and pain. The start of RA was defined as the first occurrence of joint swelling reported by the patient. The anamnesis of concomitant diseases and used antirheumatic medications (DMARD, GCS, NSAID) were gathered. Electronic health records were used to verify the onset of RA diagnosis and retrospectively assess the fulfilment of ACR/EULAR 2012 classification criteria (Aletaha et al., 2010). Smoking habits were classified as having ever smoked, including current and previous smoking anamnesis.

4.2.2. Physical examination

A standard physical examination was conducted. A certified rheumatologist assessed tender and swollen joint counts (28 and 42 joint scores) in the RA group. Height to the nearest 0.5 cm was measured with a stadiometer. Body weight was measured in kilograms with an electronic scale. Subjects were without shoes and wore light indoor clothes. Body mass index (BMI) was calculated according to the standard formula: weight in kilograms divided by height in meters squared. The following groups of BMI were formed based on the World Health Organization (WHO) criteria: normal weight (BMI: ≤24.9 kg/m2), overweight (BMI: 25–29.9 kg/m2) and obese (BMI: ≥30 kg/m2), (WHO, 1997). Both overweight and obese were classified as adiposity in analysis.

4.2.3. Muscle function tests

The 30-Second Chair Stand Test (30-CST) and the Handgrip Strength Test (HST) were used to assess and compare muscle strength. The 30-CST was used for evaluating leg muscle function. While doing the 30-CST, patients were asked to sit on a chair, with their spine straight and hands placed crossed across their chest, on opposite shoulders. On a signal, subjects rose at their own pace, to a full standing position, and then returned to seated position as many times as they were able. A 30 s trial was preceded by a practice attempt of 1–3 repetitions. The final chair-stand score was the total number of unassisted full-stands during the 30 s time (Unver et al., 2015).

The hand muscle function was assessed with HST. Grip strength was measured in bars with a calibrated Riester Dynatest dynamometer. One practice attempt was followed by three additional consecutive attempts, with pauses in between, of up to 60 s. The average value of three test trials of both hands was used for statistical analysis.

4.2.4. Patient reported nutritional assessment

A 24-hour dietary recall method was used to receive information about foods and beverages consumed during the prior 24 hours. The data was gathered to evaluate energy and nutrient intake. The received information was inserted into the NutriData software developed by the Estonian National Institute for Health Development in order to translate foods and beverages into nutrient equivalents (NutriData Software Homepage, 2018).

4.2.5. Blood samples

Blood samples were collected after an overnight fast between 8 a.m. and 11 a.m. Blood samples included measuring vitamin D (vitamin D3), calcium, OPG, parathyroid hormone (PTH), and CRP (immunoturbidimetric method). Luminex's xMAP (Luminex Corp) technology was used to evaluate IL-6, TNFa, and IL-1b.

Anti-CCP, RF and ESR (Westergren method) were analysed only in the ERA group. An electrochemiluminescence assay was used with the cutoff value of 17 kU/L for anti-CCP positivity. The immunoturbidimetric method was applied to measure RF, and was assessed positive if RF value was >14 IU/mL.

4.2.6. RA disease activity assessment

To evaluate disease activity, the number of tender and swollen joints in the ERA group were assessed (28 joint scores). DAS28 scores using CRP were calculated according to the standard formula. ERA patients were grouped as having low disease activity (DAS28 score <3.2), moderate disease activity (≥3.2 to ≤5.1) or high disease activity (>5.1) according to the DAS28 score (Anderson et al., 2012).

Radiographic progression of ERA was assessed in X-rays of hands using Sharp van der Heijde scores (evaluating the presence of joint space narrowing and erosions), (van der Heijde, 2000). A qualified and experienced radiologist evaluated the X-rays of all participating subjects. Sharp scoring applies for changes in X-rays of hands, and therefore further statistical analysis focused only on the hand region.

4.2.7. Body structure evaluation

A Lunar Prodigy DXA machine was used to separately estimate arm, leg, whole body bone mass both in ERA group and the population-based control group (Paper I–III); in Paper II hand total BMD (whole-hand DXA, all hand bones distal from the wrist joint were included in the measurement), and BMC. Foot BMD measurement was not conducted due to technical reasons. Paper III additionally measured femoral neck, trochanter, lumbar spine (1–4th lumbar vertebrae, only in ERA group), proximal and ultradistal radius BMD. In the BMD test, the T-score was a comparison of a patient's bone density with that of a healthy 30-year-old of the same gender (Lu et al., 2001).

In Paper I, III were separately measured arm and leg lean, fat mass. A qualified and experienced technician performed all DXA measurements on all participating subjects. All the conducted structural measurements and functional tests have been summarised in Table 1.

Table 1. Characteristics of study group's evaluated structural and functional measurements.

Structural measurements	Functional tests
Arm, leg, whole body bone mass	30-CST
Arm and leg lean, fat mass	Handgrip Strength Test
Hand total BMD and BMC	
Femoral neck, trochanter, lumbar spine	
BMD Proximal and ultradistal radius BMD	

BMD, bone mineral density; BMC, bone mineral content. 30-CST, 30-Second Chair Stand Test.

4.2.8. Statistical analysis

Statistical analyses were performed using Statistica version 13.3 for Windows and IBM SPSS Statistics version 27.0 for Windows.

All data were tested for normality. The continuous data were presented as mean (±SD) if distributed normally, or else by median with 25% and 75% percentiles. The unpaired two-tailed Student's t-test (for mean) and Mann-Whitney U test (for median) were used to make comparisons between ERA patients and controls.

Multiple linear regression with binary exposure variables was carried out, to assess the bone, lean, and fat mass of arms and legs, as well as the muscle function mean difference between ERA (ERA=1) and control group (control group=0). The model was adjusted for age, gender, height and weight, as ERA patients differed from controls by age and gender. Multiple linear regression analysis was done to assess in ERA the association of smoking to arms and legs bone mass; the influence of CRP and the amount of consumed proteins to lean-mass changes (Paper I).

In Paper II, multiple linear regression with binary exposure variables was used to assess hand total BMD and BMC mean difference between ERA (ERA=1) and control group (control group=0). The model was adjusted for age, gender, height, and weight, as ERA patients differed from controls by age and gender. Multiple linear regression analysis was conducted in ERA to assess the association of smoking, different inflammation markers and bone, RA disease specific markers (RF, anti-CCP) and usage of different medications (methotrexate–MTX; glucocorticoids–GCS) to hand BMD changes. Logistic regression analysis was used to assess variables predicting RA specific X-ray erosive changes (Paper II).

In Paper III, multiple linear regression with binary exposure variables was carried out to assess femoral neck, trochanter, proximal and ultradistal radius BMD; with arm, leg and trunk bone mass mean difference between ERA (ERA=1) and control group (control group=0). The model was adjusted for age, gender, height, and weight, as ERA patients differed from controls by age and gender. Multiple linear regression analysis was used to assess in ERA the association of smoking, different inflammation markers and consuming of PUFAs to BMD and bone mass changes in various skeletal regions.

Also, in Paper III multiple regression analysis (adjusted for age, gender, height, and weight) was carried out both in ERA and control subjects to evaluate if dietary intake of PUFAs was associated with arm and leg structural (fat, lean mass) changes. Additional analysis of the ERA and control group females (adjusted for age, height, and weight) was conducted to diminish gender related body structure differences.

5. RESULTS

5.1. General characteristics of the study groups

The study group consisted of 83 ERA patients and 321 control subjects. 72% of ERA subjects were female and mean age in the ERA group was 53 years (19–79). ERA patients had significantly lower weight than controls (p=0.009).

Altogether, 71% of ERA patients were anti-CCP positive and 65% were RF positive. The mean time from first RA symptoms (reported by the patients) was 88 days (48–245). Mean DAS28 score was 3.9±1.3, which corresponds to moderate disease activity according to ACR recommendations (Fleischmann, 2020). Most ERA patients (76%; 95% CI 65.3–84.6) had erosions in hand joints according to Sharp scoring. 58% of ERA patients were using disease-modifying anti-rheumatic drugs (DMARDs). Methotrexate (MTX) was the most often used DMARD (40% of the group). Moreover, 27% (22) of ERA patients used glucocorticosteroids (GCS), 71% (59) nonsteroidal anti-inflammatory drugs (NSAIDs), and additionally 25% (21) used vitamin D supplements. 34% of ERA patients and 21% of control subjects were smokers.

The inflammation markers CRP, IL-6, TNFa and IL1-b were all significantly higher in the ERA group. Median CRP and TNFa were higher in male ERA patients, compared to ERA female patients, but the difference was not statistically significant. OPG was almost two times higher in the ERA patients, as compared to control-group subjects (446 pg/mL versus 227 pg/mL, p<0.0001), (Table 2). The elevated level of OPG in ERA suggests an altered bone structure caused by the inflammation.

Table 2. Characteristics of the study groups.

	ERA patients (n=83)	Controls (n=321)	p-Value
General characteristics			
Age, years	52.7 (15.7)	47.9 (16.5)	0.018
Female gender, n (%)	60 (72)	175 (54)	0.004
Height, cm	166 (9)	171 (10)	<0.0001
Weight, kg	74.7 (14.8)	80.2 (17.6)	0.009
BMI (kg/m^2)	27.2 (5.6)	27.2 (5.3)	0.960
Smoking (ever), n (%)	28 (34)	66 (21)	0.014
Inflammation markers			
CRP mg/L	4.0 (1.6–18.0)	0.9 (0.2–2.5)	<0.0001
ESR mm/h	20.7 (20.4)	-	-
IL-6 pg/ml	2.9 (0–19.0)	0 (0–0)	<0.0001
TNFa pg/ml	2.2 (1.6–3.0)	1.8 (1.4–2.3)	<0.0001
IL-1b pg/ml	0.1 (0–1.0)	0 (0–0)	<0.0001
OPG pg/ml	446 (334–658)	227 (177–299)	<0.0001

BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin – 6; TNFa, tumor necrosis factor alpha; IL-1b, interleukin – 1 beta; OPG, osteoprotegerin. Values in table represent mean (SD) or median (with interquartile range). Note: Adapted from Valner A et al. Factors associated with hand bone changes in early rheumatoid arthritis. *Musculoskeletal care*. 2023;21(1):108–116.

5.2. Hand and leg structural and functional changes in early rheumatoid arthritis

5.2.1. Bone mass changes (Paper I)

The arm and leg bone mass of ERA subjects did not differ from the bone mass of population-based control subjects (Table 3).

Table 3. Mean estimated difference of body structure in ERA compared to controls.*

Dependent Variable	Regression Coefficient (b)	Standard Error	p-Value
Arm structure			
Arm bone mass	9.6	6.5	0.144
Arm lean mass	**-304.6**	98.8	**0.002**
Arm fat mass	**220**	62.0	**0.0005**
Leg structure			
Leg bone mass	7.5	14.0	0.618
Leg lean mass	**-943.4**	184.9	**<0.0001**
Leg fat mass	417.5	241.0	0.080

* Multiple regression models adjusted for age, gender, height and weight.
Note: Adapted from Valner A et al. Structural and Functional Changes of Hands and Legs in Early Rheumatoid Arthritis. *Medicina (Kaunas)*. 2021;57(4):317.

5.2.2. Hand and leg bone mineral density changes (Paper II)

In the ERA group, the mean hand total BMD (0.37 g/cm^2 versus 0.41 g/cm^2, p<0.0001) was significantly lower compared with control subjects. Furthermore, bone structure regression model confirmed that in ERA hand total bone mineral density was already decreased (b -0.01, p=0.045) compared to control group subjects (Table 4).

Table 4. Mean estimated difference of bone structure in ERA compared to controls.*

Dependent Variable	Regression Coefficient (b)	Standard Error	p-Value
Hand total BMD	**-0.01**	0.006	**0.045**
Hand total BMC	-0.43	0.61	0.488
Hand total Area	1.01	0.80	0.208

* Multiple regression models adjusted for age, gender, height and weight; BMD, bone mineral density; BMC, bone mineral content.
Note: Adapted from Valner A et al. Factors associated with hand bone changes in early rheumatoid arthritis. *Musculoskeletal care*. 2023;21(1):108–116.

5.2.3. Bone mineral density in different body regions (Paper III)

Despite of the absence of arthritis in the hip area, BMD in the ERA group was already significantly decreased in the femoral neck (p=0.027) and trochanter regions (p=0.012) compared with the control group subjects (Table 5). At the same time, peripheral BMD assessment of the radius area did not show significant BMD lowering in ERA compared to the controls. Nevertheless, the median T-score of our ERA patients yet indicated normal bone mineral density both in the femoral neck and lumbar spine in accordance with the classification of BMD (Lu et al., 2001).

Table 5. Characteristics of study group bone mineral density.

	ERA patients (n=83)	Controls (n=321)	p-Value
General BMD characteristics			
Femoral neck BMD, g/cm^2	0.97 (0.21)	1.02 (0.16)	0.027
Trochanter BMD, g/cm^2	0.84 (0.17)	0.89 (0.16)	0.012
Total hip BMD, g/cm^2	1.02 (0.17)	1.06 (0.16)	0.036
Lumbar L1- L4 BMD, g/cm^2	1.17 (0.18)	-	-

BMD, bone mineral density. Values in table represent mean (SD).
Note: Adapted from Valner A et al. Does Dietary Polyunsaturated Fatty Acid Intake Associate With Bone Mineral Density and Limb Structural Changes in Early Rheumatoid Arthritis? *Nutrition and metabolic insights*. 2023;16:11786388231176169.

5.2.4. Lean and fat mass changes, muscle function alterations (Paper I)

We found that ERA subjects had lower arm (b -304.6, p=0.002) and leg (b -943.4, p<0.0001) lean mass compared to controls (Table 3). Correspondingly, ERA patients had lower mean handgrip in the Handgrip Strength Test (b -0.08, p<0.0001) and worse leg muscle strength in the 30-Second Chair Stand Test (b -2.3, p=0.004) compared to control group subjects (Table 6). Arm fat mass was higher (b 220.0, p=0.0005) in ERA subjects compared with controls, but there was no difference in leg fat mass (Table 3).

Table 6. Mean estimated difference of muscle function in ERA compared to controls*

Dependent Variable	Regression Coefficient (b)	Standard Error	p-Value
Function			
Mean handgrip	**-0.08**	0.02	**<0.0001**
30-CST	**-2.3**	0.8	**0.004**

* Multiple regression models adjusted for age, gender, height and weight; 30-CST, 30-Second Chair Stand Test.
Note: Adapted from Valner A et al. Structural and Functional Changes of Hands and Legs in Early Rheumatoid Arthritis. *Medicina (Kaunas)*. 2021;57(4):317.

Overall, we found that different structural and functional changes in hands and legs were already present in early RA. Patients with early RA have lower arm and leg lean mass, and accordingly decreased muscle function. Furthermore, they also have higher fat mass in arms, but not legs. Arm and leg bone mass is not significantly decreased in early RA, but hand BMD is lower compared to the population-based control group. Moreover, regardless of the absence of arthritis, BMD in the ERA group was significantly decreased in the femoral neck and trochanter regions, but BMD of the radius area was still normal compared with the controls.

5.3. Laboratory markers associated with early rheumatoid arthritis related structural changes of hand and leg

5.3.1. Markers associated with bone changes (Paper I, III)

The inflammation markers CRP, IL-6, TNFa and IL1-b were all significantly higher in ERA subjects compared with population-based controls. Additional analysis of the ERA females and population-based control females (adjusted for age, height, and weight) was carried out to diminish gender related body structure differences. In ERA female subjects, decreased arm bone mass was associated with higher level of CRP (b -0.82*,* p=0.042). Still, no such association was noticed in ERA female leg bone mass. A separate analysis of the males was not done due to the smaller number of men participating in the study. In ERA subjects, arm and leg bone mass changes were not associated with RF positivity and OPG.

To test if associations between regional BMD changes and inflammatory markers exist, different multiple regression models were built. Still, none of these demonstrated significant associations between lumbar (Table 7), femoral neck, proximal or ultradistal radius BMD changes and different serum inflammatory markers in ERA patients. Anti-CCP positivity was associated with decreased ultradistal radius BMD (b -0.047*,* p=0.036). Separate BMD assessment of these ERA patients, who had received GCS was not done due to the small study groups.

Table 7. Summary of regression analysis for variables predicting ERA-specific lumbar BMD changes.*

Dependent Variable	Predictor Variable	Regression Coefficient (b)	Standard Error	p-Value
L1-L4 BMD	Smoking	-0.042	0.043	0.335
	CRP	-0.001	0.001	0.471
	IL-6	-0.001	0.001	0.179
	TNFa	0.012	0.009	0.147
	IL-1b	-0.005	0.009	0.582
	RF positivity	-0.078	0.042	0.069
	Proteins (g)	0.001	0.001	0.283
	PUFAs (g)	0.008	0.004	0.058

* Different multiple regression models adjusted for age, gender. BMD, bone mineral density; CRP, C-reactive protein; IL-6, interleukin-6; TNFa, tumour necrosis factor alpha; IL-1b, interleukin-1 beta; RF, rheumatoid factor. RF positive, when RF >14 IU/mL. PUFAs, polyunsaturated fatty acids.
Note: Adapted from Valner A et al. Does Dietary Polyunsaturated Fatty Acid Intake Associate With Bone Mineral Density and Limb Structural Changes in Early Rheumatoid Arthritis? *Nutrition and metabolic insights*. 2023;16:11786388231176169.

5.3.2. Markers associated with lean mass changes (Paper I)

Analysis indicated that, in ERA, the lean mass of arms and legs was negatively associated with CRP. Still, dietary intake of proteins did not have a significant effect on lean mass changes, in either hands or legs (Table 8).

Table 8. Summary of regression analysis for variables predicting ERA-specific body structural changes.*

Dependent Variable	Predictor Variable	Regression Coefficient (b)	Standard Error	p-Value
Arm lean mass	CRP	**-11.13**	3.5	**0.0002**
	Proteins	-0.6	2.7	0.824
Leg lean mass	CRP	**-18.6**	9.2	**0.047**
	Proteins	6.0	7.1	0.403

* Different multiple regression models adjusted for age, gender, height and weight.
Note: Adapted from Valner A et al. Structural and Functional Changes of Hands and Legs in Early Rheumatoid Arthritis. *Medicina (Kaunas).* 2021;57(4):317.

5.4. Variables predicting BMD changes and RA specific X-ray erosive changes in early rheumatoid arthritis (Paper II)

The majority of our ERA patients had erosions in hand joints according to Sharp scoring. In ERA patients, total hand BMD changes were not associated with the appearance of erosions (Table 9).

Table 9. Summary of regression analysis for variables predicting ERA-specific hand total BMD changes.*

Dependent Variable	Predictor Variable	Regression Coefficient (b)	Standard Error	p-Value
Hand total BMD	Smoking	0.007	0.015	0.621
	BMI	0.002	0.001	0.075
	CRP	-0.001	0.0004	0.073
	IL-6	**-0.0005**	0.0002	**0.024**
	TNFa	-0.003	0.003	0.332
	IL-1b	-0.002	0.003	0.442
	Ca	0.014	0.032	0.659
	25 (OH) Vitamin D	**0.001**	0.0003	**0.002**
	OPG	-0.00001	0.00002	0.651
	PTH	-0.00001	0.00003	0.722
	RF positivity	**-0.033**	0.014	**0.021**
	Anti-CCP positivity	-0.018	0.015	0.242
	Using MTX	0.006	0.013	0.677
	Using GCS	-0.015	0.014	0.289
	Presence of erosions	-0.004	0.019	0.841
	Proteins (g)	0.0002	0.0003	0.408

* Different multiple regression models adjusted for age, gender. BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; OPG, osteoprotegerin; PTH, parathyroid hormone; RF, rheumatoid factor. RF positive, when RF >14 IU/mL; Anti-CCP, anti-citrullinated protein antibodies. Anti-CCP positive, when ≥17 kU/L. MTX, methotrexate; GCS, glucocorticoids.
Note: Adapted from Valner A et al. Factors associated with hand bone changes in early rheumatoid arthritis. *Musculoskeletal care*. 2023;21(1):108–116.

In ERA subjects, decreased hand total BMD was associated with lower 25 (OH) Vitamin D level (b 0.001, p=0.002), RF positivity (b -0.033, p=0.021) and higher IL-6 (b -0.0005, p=0.024) value. However, OPG, CRP, using of GCS and anti-CCP positivity did not seem to have significant association with hand total BMD (Table 9).

Survey of only ERA patients indicated that an increased likelihood of having RA specific erosive changes in hand X-rays was associated with increasing BMI and smoking. Smokers were 10 times more likely to already have RA specific hand X-ray changes in the early phase of disease. The presence of anti-CCP and RF positivity did not relevantly contribute to early arthritis erosive changes in hands. While analysing laboratory markers for targeting treatment, we found that the level of inflammation (CRP, IL-6, TNFa, IL-1b) as well as the amount of consumed proteins did not seem to have significant effect in ERA on the appearance of X-ray detected erosions (Table 10).

Table 10. Summary of logistic regression analysis for variables predicting RA specific X-ray erosive changes.*

Dependent Variable	Predictor Variable	OR (95% CI)	p-Value
X-ray detected erosions	BMI (kg/m2)	**1.17 (1.01–1.36)**	**0.036**
	Smoking (ever)	**9.74 (1.44–66.06)**	**0.020**
	CRP	0.98 (0.94–1.02)	0.362
	IL-6	1.00 (0.98–1.03)	0.903
	TNFa	0.83 (0.65–1.06)	0.139
	IL-1b	0.80 (0.60–1.06)	0.122
	OPG	0.99 (0.99–1.00)	0.090
	RF positivity	0.67 (0.15–2.99)	0.602
	Anti-CCP positivity	0.31 (0.05–1.83)	0.198
	Proteins (g)	1.02 (0.99–1.05)	0.249
	Arms bone mass (g)	1.00 (0.99–1.01)	0.942

* Different logistic regression models adjusted for age, gender. BMI, body mass index; CRP, C-reactive protein; OPG, osteoprotegerin; RF, rheumatoid factor. RF positive, when RF >14 IU/mL; Anti-CCP, anti-citrullinated protein antibodies. Anti-CCP positive, when ≥17 kU/L.
Note: Adapted from Valner A et al. Factors associated with hand bone changes in early rheumatoid arthritis. *Musculoskeletal care*. 2023;21(1):108–116.

5.5. Dietary habits associated with hand and leg structural changes in early rheumatoid arthritis (Paper I, II, III)

ERA patients consumed fewer calories, proteins and fats (including polyunsaturated fatty acids) compared with controls, ($p<0.005$). Still, there was no significant difference in consumption of carbohydrates and alcohol between ERA patients and controls. Therefore, the further analysis concentrated on the evaluation of associations between dietary intake of PUFAs, proteins and hand, leg structural changes in ERA.

Regression analysis of the ERA group showed that only higher lumbar BMD was associated with greater dietary consumption of PUFAs (b 0.008, p=0.058), (Table 7). In both the ERA and control groups, arm and leg bone mass changes were not associated with dietary intake of PUFAs. Furthermore, there was no association between arm and leg lean mass changes and dietary intake of PUFAs.

Still, multiple regression analysis of the ERA group (adjusted for age, gender, height, and weight) indicated that lowering of arm fat mass was associated with elevated dietary consumption of PUFAs (b -28.17, p=0.020). At the same time, PUFA intake didn't show significant effect on arm fat mass in the control group (Table 11). Additional analysis of the ERA and control group females (adjusted for age, height and weight) verified the same results: only in ERA females was arm fat mass reduction associated with higher intake of PUFAs (b -35.50, p=0.016). An analysis of the ERA females and population-based control females was carried out to diminish gender related body structure differences. A separate analysis of males was not done due to the smaller number of men participating in the study.

Contrastingly, dietary intake of PUFAs didn't show association with leg fat mass changes both in the ERA and controls, including female subjects. This suggests that in ERA, the decrease of arm fat mass was associated with higher dietary consumption of PUFAs, and the result was not influenced by some other factor, as the statistical models were adjusted.

Table 11. Summary of regression analysis for variables predicting ERA-specific body fat changes.*

Dependent Variable	Predictor Variable	Regression Coefficient (b)	Standard Error	p-Value
ERA arm fat mass	PUFAs (g)	**-28.17**	11.88	**0.020**
Control arm fat mass	PUFAs (g)	-2.23	3.31	0.501

* Different multiple regression models adjusted for age, gender, height and weight.
PUFAs, polyunsaturated fatty acids.
Note: Adapted from Valner A et al. Does Dietary Polyunsaturated Fatty Acid Intake Associate With Bone Mineral Density and Limb Structural Changes in Early Rheumatoid Arthritis? *Nutrition and metabolic insights*. 2023;16:11786388231176169.

In both ERA and controls, as in female groups, dietary intake of proteins did not associate with bone mass changes both in arms and legs, or with hand total BMD (Table 9) or lumbar BMD changes (Table 7). Moreover, the amount of dietary consumed proteins did not associate with ERA hand or leg lean mass changes (Table 8).

5.6. Smoking habits associated with hand and leg structural changes in early rheumatoid arthritis (Paper I, II, III)

Smoking is a health hazard. In ERA subjects, arm and leg bone mass changes were not associated with smoking (Table 12). Smoking did not also seem to have significant effect on hand total BMD (Table 9) nor on femoral neck, proximal or ultradistal radius BMD. Moreover, it also did not have a significant effect on muscle structural and functional changes, both on hands and legs.

Table 12. Summary of regression analysis for variables predicting ERA-specific body structural changes.*

Dependent Variable	Predictor Variable	Regression Coefficient (b)	Standard Error	p-Value
Arm bone mass	Smoking	14.7	12.3	0.237
Leg bone mass	Smoking	31.0	25.4	0.226

* Different multiple regression models adjusted for age, gender, height and weight.
Note: Adapted from Valner A et al. Structural and Functional Changes of Hands and Legs in Early Rheumatoid Arthritis. *Medicina (Kaunas).* 2021;57(4):317.

Summary of structural and functional changes of hands and legs in ERA

HANDS

- BONE MASS: not significantly decreased in ERA.
- Hand BMD: ↓ in ERA.
    - ↓ associated with higher serum level of IL-6 and positive RF.
    - Hand BMD changes were not associated with the occurrence of erosions.
- EROSIONS
    - Smoking habits↑ the RA-specific erosive changes risk 10x.
    - Higher BMI↑ the RA-specific erosive changes risk.
- LEAN MASS: lean mass↓ and decreased muscle function in ERA.
    - ↓ associated with higher level of CRP.
- FAT MASS: ↑ in ERA.
    - ↓associated with elevated dietary intake of PUFAs.

LEGS

- BONE MASS: not significantly decreased in ERA.
- LEAN MASS: lean mass↓ and decreased muscle function in ERA.
    - ↓ associated with higher level of CRP.
- FAT MASS: no significant change in ERA.

6. DISCUSSION

6.1. Hand and leg structure and function in early rheumatoid arthritis

The concept of "early rheumatoid arthritis" aims to promote early diagnosis and aggressive treatment to avoid or postpone major structural damage and improve quality of life. The speed of development of respective changes has received more attention in recent research. Our study was undertaken to find out if there are different structural and functional changes of upper and lower limbs already present in ERA and if the changes in hands and legs are similar. We also evaluated factors associated with these arthritis-related hand and leg structural and functional changes in early rheumatoid arthritis.

The results of the study (Paper I) imply that there are structural and functional changes of hands and legs already present in the early stage of RA, and these changes do not develop simultaneously. Our patients were assessed when they were first referred to a rheumatologist consultation. In average, it occurred 88 days after the onset of the first symptoms. We found that 76% of patients already had hand erosions at this early phase. However, as our study indicated, arm and leg bone mass was not significantly decreased in early RA compared with the population-based control group. This is in contrast to findings by Forslind et al. (2003), who reported a bone mass decrease just a few months after disease onset. The difference could have resulted from the other study only measuring bone mass in the trochanter area of the femur. Another study of inflammatory arthritis patients by Brunet et al. (2021) failed to find a decrease in bone mass using high-resolution peripheral quantitative computed tomography.

While bone mass assessment using DXA provides a composite measure of bone size and mineral density (DiMeglio et al., 2013), bone mineral density is defined as the amount of minerals contained in a specific area of bone (Clasey et al., 1997). Bone mass is considered a determinant of bone strength (DiMeglio et al., 2013) and BMD assessment is used to screen for the presence of osteoporosis. As a decrease in bone mass and BMD may already appear in the early stage of RA (Daragon et al., 2001; Forslind et al., 2003; Hill et al., 2010), it is crucial to identify different bone alterations as early as possible. Our study confirmed that in ERA there is already a very early decrease in hand BMD. Prior research has also demonstrated a hand BMD decrease in ERA (Haugeberg et al., 2007; Black et al., 2014; Szentpetery et al., 2016; Ziegelasch et al., 2017). Still, our research showed a significant BMD decrease already at the time of diagnosis, meaning that the BMD change in our ERA patients occurred earlier than found in previous research. As the median time from the clinical manifestation of RA symptoms of our ERA subjects was 88 days, this indicates the presence of a decrease in hand BMD already in a very short duration of RA. This is relevant finding, as it has been stated before that the accelerated hand BMD loss in the first year of RA is related to progressive joint damage in both hands and feet. Hand BMD lowering in the first year of ERA predicts future progressive joint damage (Güler-Yüksel et al., 2010). Furthermore, recent research using digital X-ray radiogrammetry has suggested that BMD lowering in metacarpal bones already in the first three months of ERA could independently predict radiographic joint damage after just one year of arthritis (Ziegelasch et al., 2017). In ERA, lowering of hand BMD may be the earliest sign caused by inflammation and may precede the occurrence of erosions (Black et al., 2014). At present, assessment of hand BMD is not a standard procedure in ERA. Accounting for the findings of our study, we propose hand BMD evaluation as an additionally beneficial procedure for observing disease activity. Additionally, without the presence of clinically active arthritis, the axial skeleton BMD of our ERA subjects was also significantly decreased compared with controls, indicating the systemic effect of inflammation. A previous study by Sahin et al. (2006) also reported lumbar and femoral neck BMD lowering in female RA subjects. We thus demonstrated that the bone changes occur very early in the development of the disease.

In our ERA patients, the most noticeable changes were in limb lean mass, specifically their prevalent reduction. The predominant change in leg lean mass is possibly due to anatomy, as the muscle mass of legs is greater than that in hands, and therefore the decrease in leg muscle mass due to inflammation can be more evident. Correspondingly, ERA subjects had significantly worse muscle function of hands in HST and legs in the 30-S CST. The results suggest that leg muscle function is already impaired at the early stage of RA due to lower leg lean mass. Furthermore, in ERA subjects, mean handgrip may also decrease due to reduced arm lean mass. Our results confirmed previous research demonstrating that ERA patients had lower muscle volume compared with control subjects, indicating the appearance of muscle atrophy in RA (Turk et al., 2018; Farrow et al., 2021). In ERA, hand bone loss in the first six months of disease duration is considered to predict poor hand function at a five-year follow-up (Deodhar et al., 2003; Haugeberg et al., 2006). As muscle strength plays an important role in preventing RA-related bone loss (Liphardt et al., 2020), it is crucial that ERA patients be physically active. However, our study was the first to separately evaluate hand and leg lean mass in ERA, and show that in both areas, lean mass and function decrease in parallel.

Our study shows that ERA patients had higher arm fat mass, but no significant difference in leg fat mass compared with control group subjects. The change in leg fat mass may not be so evident due to anatomical reasons. It is possible that muscle mass decrease in legs and increase of fat mass without body weight changes is not yet so evident in legs as they have greater muscle mass. A study by Turk et al. (2018) also reported that longer symptom duration in ERA was associated with an increased body fat mass (Turk et al., 2018). Still, our study was the first to show that in ERA there is only a relevant increase of hand, but not leg, fat mass. The data suggest that in ERA, lean mass may lower due to the inflammation, and as a result possibly increase the proportion of arm fat.

RA inflammatory activity is mainly assessed using the DAS28 score, although it does not cover feet (Andersson et al., 2021). However, foot joint involvement is common in ERA (Michelson et al., 1994; Stolt et al., 2017; Andersson et al., 2021), impacting everyday life and coping (Williams et al., 2012; Stolt et al., 2017). Furthermore, after 3 years of disease duration, up to 20% of cases have RA-related radiographic joint damage of hand and feet joints (van der Heijde et al., 1992). A study of ERA subjects indicated that erosions were similarly apparent both in hand and leg joints (Boutry et al., 2003; Calisir et al., 2007) and 77% of patients had erosive changes in MTP joints (Boutry et al., 2003). In our ERA subjects, we only used hand X-rays to evaluate erosive joint destruction, so we therefore cannot assess the extent of leg joint damage. Still, we found a majority (76%) of our ERA subjects already had erosive changes hand X-rays in the early stage of disease, suggesting an active disease.

In RA, the causes of joint damage may differ between hand and leg joints, as shown by differences in radiographic damage according to Sharp van der Heijde scoring (Terao et al., 2015). For that reason, in ERA, additional separate assessments of the legs in addition to hands offers an extra tool allowing earlier and more precise diagnosis, and via it enabling earlier treatment.

6.2. Inflammatory markers association with hand and leg structural, functional changes in early rheumatoid arthritis

While assessing the associations between hand and leg structural and functional changes with inflammatory markers in ERA, we found significantly higher levels of OPG compared with controls. We also noticed a tendency for OPG to be higher in patients with clinically active arthritis according to DAS28 scoring. This means that in the presence of a higher DAS28 score, OPG levels were also elevated, suggesting the effects of inflammation. That is in line with the results of a recent meta-analysis, which showed that the level of OPG was positively associated with RA disease duration and activity, BMI (Wang et al., 2017). Soliman et al. (2024) also found a positive correlation between the serum OPG and the synovitis in RA. It has been suggested that the levels of OPG may vary at different RA disease stages, being elevated in ERA, but not in longstanding disease (Liu et al., 2010; Soliman et al., 2024). Also, OPG is influenced by testosterone. In men, testosterone inhibits production of OPG (Bianchi, 2018). Compared to normal-weight controls, obese women had significantly lower serum concentrations of OPG. Furthermore, additional weight lowering resulted in further decrease of OPG serum concentrations (Holecki et al., 2007). Surprisingly, our ERA female patients had higher levels of OPG, possibly due to higher total body fat mass and lower testosterone levels, compared to males. OPG was measured in our RA patients, as it may possibly be a sensitive method for detection of active bone and cartilage destruction in RA (Karsdal et al., 2011; Soliman et al., 2024). In our ERA patients, arm and leg bone mass changes were not associated with OPG, possibly due to the early stage of RA disease. Nevertheless, the results of our research confirmed the previous data of higher OPG level in the early phase of RA and the tendency of OPG to be elevated in active arthritis. Therefore, OPG could be considered an additional diagnostical marker suggesting inflammatory activity and active joint damage in RA.

In our ERA patients, lower lean mass of arms and legs was associated with higher CRP value, suggesting the systemic effect of inflammation. Similarly, Koo et al. (2020) found that patients with long-standing RA had lower appendicular lean mass, which correlated with higher disease activity. Furthermore, our ERA subjects also had higher hand fat mass. Still, the increase of leg fat mass was not so evident. Our results confirm the previous research, that RA related inflammation is related to lowering of muscle mass in a stable or increased fat mass (Engvall et al., 2008), being present already in the early stage of RA (Gioia et al., 2020). Additionally, RA-patients had differing tissue structure in arms and legs compared to the general population (Koo et al., 2020). Moreover, it was reported that muscle wasting in RA was more likely to appear in subjects with higher disease activity (Mochizuki et al., 2019; Baker et al., 2021; Ångström et al., 2023); low body weight, waist circumference and BMI (Ångström et al., 2023). As anticipated, in our ERA patients muscle loss was associated with worsening of physical function that was also reported in other studies (Baker et al., 2021; Ångström et al., 2023) indicating the systemic nature of RA disease. For that reason, early diagnosis and treatment is necessary to avoid muscle loss caused by inflammation.

6.3. Hand bone mineral density and appearance of arthritis related erosions in early rheumatoid arthritis

In paper II, we aimed to assess if hand bone mineral density is related to the appearance of arthritis associated erosions. A qualified and experienced radiologist evaluated hand X-rays of all ERA subjects to identify the presence of erosions. In later analysis, the findings were stratified as the erosive changes were present or not. We discovered that more than 70% of our ERA patients already had erosions in the early stage of disease and hand BMD was also lowered due to ERA. Nevertheless, we did not observe an association between hand BMD changes and erosion presence.

Periarticular osteoporosis can already be present in ERA (Alenfeld et al., 2000). Hand BMD lowering may appear before the manifestation of erosions and hand BMD loss has itself been previously associated with increased predisposition to erosive changes (Black et al., 2014). Erosions are associated with juxta-articular bone loss (Arboleya et al., 2013; Guo et al., 2018; Llorente et al., 2020). Additionally, the presence of erosions and wrist BMD decreases in ERA is associated with longer disease duration (Wang et al., 2015). In our ERA patients, the median time from the clinical manifestation of RA symptoms was only 88 days. Possibly, therefore, the results of our study did not show association between a decrease in hand BMD and the appearance of erosions in ERA, due to the short-term duration of arthritis. The finding is in accordance with the data reported by Ziegelasch et al. (2017), that early hand BMD decrease alone could predict radiographic joint damage (including erosive changes) only after one year of disease onset. Still, the absence of the association in the early stage does not mean that the finding will not possibly appear in the later phase of RA. In ERA, erosions are just probably small and therefore the association between hand BMD changes and presence of erosions is not relevant. Moreover, a recent study also found that in RA carpus, metacarpal bones, and phalanges BMD was also lowered (Brance et al., 2023). Therefore, it is also possible that the association between hand BMD lowering and the appearance of erosions in our ERA patients was not so evident, as we did not conduct additional DXA of the juxta-articular region (metacarpal bones), the region that is associated with bone erosions. Early BMD lowering may predict poor functional outcome (Deodhar et al., 2003), still currently in ERA, hand BMD assessment is not a standard procedure. The data of our conducted study suggest that in ERA, hand BMD evaluation could also be a useful method for rheumatologists for monitoring the course of the disease. Furthermore, considering the data, we suggest hand BMD evaluating at the diagnosis of RA, especially for patients who do not have erosive changes in hand X-rays.

6.4. Markers related to hand bone mineral density lowering and RA specific X-ray erosive changes in early rheumatoid arthritis

The second paper also focused on finding laboratory markers that might relate to hand bone mineral density lowering and erosive changes in early rheumatoid arthritis. The markers associated with ERA with a decrease in hand BMD, and the appearance of erosions, were different.

Vitamin D may affect the immune system (Medrano et al., 2018) and its deficiency can lead to osteoporosis (Tomizawa et al., 2019; Kwon et al., 2020). In our ERA patients, lower total hand BMD was associated with lower serum 25 (OH) Vitamin D levels. The results of our study are in accordance with previous data suggesting vitamin D levels are important in ERA. Still, these associations need further research, as the measuring of vitamin D in our study was not on a specific season due to the long-term gathering of the study groups, and some ERA patients used Vitamin D supplements. Recent studies have reported that patients with more active RA had a lower serum vitamin D level (Zakeri et al., 2016; Tv et al., 2023). Vitamin D can reduce tender joints count and via it influence the DAS28 score (Chandrashekara et al., 2017; Guan et al., 2020).

Our results on the presence of RF confirmed the previous data, which showed that hand BMD changes were negatively associated with RF positivity, suggesting the systemic nature of RA. A recent study reported that the presence of RF in RA is associated with low BMD, especially in the femoral neck (Sargın et al., 2019). Furthermore, in the presence of high RF levels, systemic BMD may already be reduced in patients with ERA (Bugatti et al., 2016).

We did not find an association between anti-CCP positivity and hand BMD lowering, presumably due to the early stage of RA disease studied. Our results were in line with previous research concerning metacarpophalangeal joints BMD (Llorente et al., 2017; Regueiro et al., 2018). In our ERA patients, the presence of erosions itself did not seem to have a relevant impact on hand BMD. Furthermore, anti-CCP and RF positivity also did not contribute notably to early arthritis erosive changes of hands in our ERA subjects, possibly due to the early stage of disease.

Pro-inflammatory cytokines, specifically TNF, IL-1, and IL-6, play an important role in the pathogenesis of inflammation-mediated bone loss (Takayanagi et al., 2000) by increasing bone resorption (Sargın et al., 2019). Furthermore, IL-6 has a direct impact on general and local bone loss (Llorente et al., 2020), leading to erosive changes via elevating RANKL expression (Kondo et al., 2017). A recent study reported that higher IL-6 plasma levels were associated with a higher risk of erosiveness (Fedele et al., 2018). The results of our study indicated that only IL-6 was negatively associated with hand BMD changes. The data is in accordance with previous research demonstrating that IL-6 has a crucial destructive role in RA and osteoporosis (Blanchard et al., 2009). Hand BMD evaluation together with the serum level of IL-6 could possibly be an additional method for selecting out ERA patients, who need earlier aggressive treatment. Contradictorily, IL-6 did not seem to have significant effect on the occurrence of erosive changes in our ERA subjects. Furthermore, the level of CRP, TNFa, IL-1b also did not seem to have relevant effect on the appearance of X-ray detected erosions in ERA. The associations were not evident possibly due to the early phase of RA disease.

Moreover, the value of OPG was also elevated in our ERA subjects, possibly due to systemic inflammation. We tried to find associations between OPG and BMD, as well as erosive changes, as the osteoclastogenesis (mediated via the RANKL/OPG route) has an essential part in the development of erosions and periarticular osteoporosis in RA (Haugeberg et al., 2003). Still, the level of OPG itself did not seem to have relevant impact on hand BMD nor on the appearance of erosive changes on X-ray of hands, possibly due to the early stage of arthritis.

The results of our study indicated that increasing BMI was associated with an increased likelihood of having RA specific erosions in hand X-rays, differently from previous research (Vidal et al., 2015; Rydell et al., 2018; Rydell et al., 2021). Nevertheless, our results are supported by the data of a metanalysis, reporting that higher BMI was related with an elevated risk of RA (Ohno et al., 2020) and possibly with a more erosive RA disease subset, as inflammatory cytokines are also produced by adipocytes. Furthermore, adiposity itself was associated with elevated inflammatory markers (Giles et al., 2008). Still, we did not find an association between BMI and hand BMD changes.

6.5. Hand and leg structural change association with dietary and smoking habits in early rheumatoid arthritis

In papers I–III we aimed to identify if hand and leg structural changes in early rheumatoid arthritis associate with dietary and smoking habits. Several studies have reported that nutritional factors have a role in RA (Khanna et al., 2017). Therefore, dietary and smoking habits were chosen for the analysis, as they are modifiable lifestyle habits by the patients themselves.

6.5.1. Dietary habits

The dietary consuming of PUFAs could alleviate RA symptoms (Kim et al., 2018), especially omega-3 PUFAs, which have well documented anti-inflammatory effects (Yates et al., 2014). In our study, higher lumbar BMD showed a strong tendency to be related to higher consumption of PUFAs. The result is in accordance with previous data showing that an elevated ratio of omega-3/omega-6 fatty acid in diet can be regarded as a defensive element against BMD lowering (Albertazzi et al., 2002; Navarini et al., 2017). Nevertheless, the association may have been weaker in our ERA subjects, as they consumed less fats compared with control subjects and it is possible that some subjects underreported nutrition in their 24-hour dietary recall interviews.

The supplementation of omega-3 fatty acids has also been found to have positive effects in maintaining muscle mass (Tachtsis et al., 2018; Cena et al., 2020) and strength (Bird et al., 2021; Ma et al., 2021), as well as physical performance (Therdyothin et al., 2023). Our ERA subjects' arm and leg lean mass changes did not relate to dietary consumption of PUFAs. We believe this was due to the short duration of arthritis.

However, the arm fat mass decrease of our ERA subjects was associated with increased dietary consumption of PUFAs, indicating the antioxidative effects of PUFAs (Richard et al., 2008). Contrastingly, leg fat mass changes did not show significant associations with intake of PUFAs, possibly due to anatomical reasons. Still, PUFA supplementation is already an official recommendation in France to RA patients for symptomatic relief (Daien et al., 2022). Considering the possible positive effect of its supplementation, it could be considered a recommendation in other countries. Omega-3 PUFAs could especially be recommended to ERA patients.

The lowering of lean mass of arm and leg in our ERA subjects was not related to a lower protein intake. Furthermore, in our patients, the amount of consumed proteins did not also seem to have a significant impact on hand BMD changes, nor on the occurrence of RA-specific erosions. This is probably due to the short duration of RA. Additionally, it may be possible that some subjects underreported their nutrition in the 24-hour dietary recall interview, and therefore the associations were not evident.

6.5.2. Smoking habits

Smoking is a risk factor for lower BMD both in the general population and in RA (Llorente et al., 2020). Furthermore, cigarette smoke may also have a negative impact on cartilage metabolism and thus increase the risk of articular cartilage loss (Amin et al., 2007). In our ERA subjects, BMD changes due to smoking habits were not significant, due to the short duration of RA disease. Still, we noticed that among our ERA patients, smokers were 10 times more likely to already have RA-specific erosive hand X-ray changes in the early stages of disease. The finding is in accordance with previous data that smoking is a risk factor for progression of erosive changes (van der Linden et al., 2009; Llorente et al., 2020; Elzorkany et al., 2021).

6.6. Summary

Combined hand and leg structural and functional changes in ERA, as well as the factors that associate with these changes, are not often the focus of medical studies, resulting in a research gap. In clinical practice, hand involvement is the frequent reason for rheumatologist appointments, as hand joint complaints may be more disabling, interfere with normal hand function, and thus greatly impair quality of life. Furthermore, hands are typically more examined, have more diagnostic procedures conducted, and even the most commonly-used scales exclude the small joints of legs while assessing arthritis activity. Still, in RA, the structural and functional changes of both hands and legs can cause remarkable decreases in quality of life. Therefore, our study of separate assessment of hand and leg structural and functional alterations, in addition to the markers that might be related to these changes, was conducted to better understand the course of ERA. Our findings demonstrate early RA already features differing structural and functional changes to hands and legs, indicating the systemic influence of inflammation. ERA patients have decreased lean mass of arm and leg, and correspondingly an impaired muscle function. Moreover, they also have higher arm (but not leg) fat mass. Arm and leg bone mass is not yet considerably lowered in ERA, but hand BMD was already decreased compared with our population-based control group. Higher inflammatory activity in ERA is associated with lower arm and leg lean mass, as well as decreased hand BMD. Reduced hand BMD is related to lower Vitamin D levels. Furthermore, in ERA, higher consumption of PUFAs is associated with lower arm fat mass. OPG could be considered as an extra diagnostical marker when evaluating inflammatory activity and joint damage in the early phase of rheumatoid arthritis.

Arthritis involvement may differ among patients. Thus, it is relevant in ERA to evaluate hands and legs in parallel. As a practical implication, an additional assessment of hand BMD and muscle mass together with evaluation of serum level IL-6 could enable to personalize dietary and training suggestions for the ERA patients and help to select better treatment strategies.

7. STRENGTHS AND LIMITATIONS

The strength of our study is that the median time from the clinical manifestation of RA symptoms was 88 days in our ERA patients, indicating that enrolled subjects had a very short duration of RA disease, enabling us to better examine patients in the early stage of the RA disease. It can also be considered a strength that we examined the structural and functional changes in ERA in parallel in upper and lower limbs, obtaining a better overview of the various changes that appear in different areas.

There are some limitations of our research that should be acknowledged and taken into consideration when interpreting the results. Our study was limited by small study groups, due to the small total size of the Estonian population. The gender differences of the study groups (ERA and controls) can also be regarded a limitation, although, we tried to match them as much as possible by adjusting models for age, gender, height, and weight.

In paper we did not assess the level of sex hormones, which can possibly alter RA's disease course.

The study's short period of nutritional assessment (24 hours) was an additional limitation. Considering the low mean amount of consumed calories in the study group, it is possible that some subjects underreported their nutrition in the 24-hour dietary recall interview. Nevertheless, the statistical analysis confirmed a significant association between the consumption of dietary PUFAs and a reduction in arm fat mass in ERA subjects. The finding was relevant and not influenced by some other factor, as the statistical models were adjusted accordingly.

8. FUTURE PERSPECTIVES

Our research indicates that in ERA, hand BMD is already decreased and elevated serum values of IL-6 associate with lower hand BMD. Presently, hand BMD assessment is not a standard procedure in early stage of RA. Measuring IL-6 values together in evaluating hand BMD could be advantageous for monitoring disease activity and be an additional method for finding ERA patients needing earlier aggressive treatment. Future studies should also explore leg BMD changes in ERA and the changes association with inflammatory markers.

Our results also demonstrated that in ERA, lean mass of hands and legs was already decreased, as well as was the corresponding muscle function impaired due to inflammation. Future research should focus on exploring limb structural change associations with other markers.

OPG levels were significantly higher in the ERA group. As OPG may potentially be a sensitive method for detection of active joint damage in RA, further research is needed to confirm its benefit in everyday practice.

Our data also showed the beneficial effect of dietary choices in ERA. A diet rich in PUFAs could alleviate RA related structural changes to extremities. Promoting healthy dietary practices could be beneficial in ERA, still additional clinical trials are needed.

The research revealed that there are structural and functional changes of extremities already present in early phase of RA, indicating the relevance of early diagnostics and early treatment. Healthy nutritional habits and lifestyle changes can potentially improve health outcomes.

9. CONCLUSIONS

1. Different structural and functional changes of hands and legs are already present in majority of patients with early rheumatoid arthritis (ERA) at the time of diagnosis (aim 1).
2. Patients with ERA have lower lean mass of arms and legs and, accordingly, decreased muscle function. Furthermore, they also have higher fat mass of arms, but not legs. Arms and legs bone mass is not significantly decreased in early RA, but hand bone mineral density (BMD) is already lowered compared with the population-based control group (aim 1).
3. The lowering of lean mass of arms and legs in early RA is associated with higher inflammatory activity, reflecting systemic nature of RA damage (aim 2).
4. The appearance of erosions in early RA is not associated with hand BMD changes, even though a majority of early RA patients already have erosions in the early stage of disease (aim 3).
5. The factors that associate with hand BMD lowering and appearance of erosions in early RA are dissimilar. Decrease of hand BMD is associated with higher value of IL-6 and positive rheumatoid factor. At the same time, lifestyle factors such as a higher body mass index score and smoking habits are associated with an increased likelihood of having erosive changes in hand X-rays. Smoking habits raise the erosive changes appearance risk by a factor of 10 (aim 4).
6. Out of dietary factors studied, only higher consumption of polyunsaturated fatty acids (PUFAs) is associated with a reduced arm fat mass. Smoking habits do not seem to have relevant effect on bone mass, muscle structural and functional changes, both on hands and legs in early RA (aim 5).

The findings of this study help to clarify the profile of some factors associated with hand and leg structural changes in early RA. Hand BMD lowering, symmetrical reduction of hand and leg lean mass as well as increase of hand fat mass can be early alterations in RA. As arthritis involvement may vary, it is relevant in ERA to evaluate hands and legs in parallel. Lower hand BMD is associated with lower serum 25 (OH) Vitamin D levels, indicating the need to already measure Vitamin D in the early phase of RA. Furthermore, OPG could be regarded an additional diagnostical marker suggesting, inflammatory activity and active joint damage in RA.

In addition to the usual X-ray of hands, assessment of hand BMD and muscle mass in conjunction with evaluation of serum level IL-6 could permit better profiling of ERA patients and choosing more comprehensive and effective treatment strategies.

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11. SUMMARY IN ESTONIAN

Jäsemete strukturaalsed ja funktsionaalsed muutused varase reumatoidartriidi korral

Reumatoidartriit (RA) on krooniline autoimmuunne haigus, mis mõjutab peamiselt käte ja jalgade väikeseid liigeseid (Scott *et al.*, 2010). See haigus esineb kõige sagedamini naistel ja vanemaealistel, mõjutades kuni 1% elanikkonnast. Haigusest tingituna tekivad sünoviit, luuerosioonid, samuti keha lihas-, rasv- ja luukoe strukturaalsed muutused (Xu *et al.*, 2021; Zeng *et al.*, 2021). Osteoporoos on RA korral sageli kaasuv haigus (Hauser *et al.*, 2014; Wade *et al.*, 2014). Periartikulaarne osteoporoos või osteopeenia on jäsemete luukahjustusele viitavad varased spetsiifilised muutused, mis eelnevad erosioonide tekkele (Kilic *et al.*, 2015). RA foonil tekkivate strukturaalsete ja funktsionaalsete muutuste patofüsioloogilised mehhanismid on keerulised ning pole veel täielikult selged. RA riskifaktoriteks peetakse reumatoidfaktori (RF) ja tsüklilise tsitrulleeritud peptiidi vastaste antikehade (anti-CCP) positiivsust, suitsetamist ning ülekaalulisust (Scott *et al.*, 2010; Turk *et al.*, 2018). Anti-CCP positiivset RA vormi peetakse erosiivsemaks haiguse vormiks (van der Linden *et al.*, 2009). Pärilikud faktorid võivad mõjutada kuni 50% juhtudest (Scott *et al.*, 2010).

Ehkki RA ravi on muutunud efektiivsemaks ja kättesaadavamaks, kujuneb 70% artriidispetsiifiline luukahjustus juba esimese kolme haigusaasta jooksul (van der Heijde *et al.*, 1995). Kuni 25%-l haigetest võib tekkida luuline kahjustus juba esimese kolme haiguskuu jooksul (Nell *et al.*, 2004). Lihasmassi vähenemine, eeskätt jäsemetel, ja rasvamassi suurenemine, peamiselt kehatüvel, stabiilse kehakaalu juures tekib kuni kahel kolmandikul RA patsientidest (Book *et al.*, 2009; Challal *et al.*, 2016).

Vaatamata RA süsteemsele olemusele ei pruugi strukturaalsed ning funktsionaalsed muutused haiguse varases faasis kätes ja jalgades paralleelselt kujuneda. Me ei leidnud uuringuid, mis võrdleksid neid esmaseid muutusi jäsemetes, siiski võivad muutused olla olemas juba pikka aega enne reumatoloogi vastuvõtule pöördumist, isegi enne kliiniliste sümptomite teket. Uuringutega on näidatud, et varajane diagnoos ning varajane ravi parandavad oluliselt patsiendi elukvaliteeti. Ei ole olemas häid ning üldtunnustatud markereid varase artriidi kulu prognoosimiseks. Kehastruktuuri muutustega seostuvad markerid tekitavad kasvavat huvi varase RA progressiooni mõistmiseks. Sageli kasutatav luudensitomeetria (DXA) võimaldab hinnata eraldi käe ja jala luu-, lihas- ning rasvamassi, aga ka luutihedust. Jäsemete varaste strukturaalsete ja funktsionaalsete muutuste kindlaks tegemine võib olla uus moodus prognoosimaks haiguse kulgu ning aktiivsust. Juba RA esimestel kuudel esinev käeluude mineraalaine tiheduse vähenemine võib ennustada RA-ga seotud liigesekahjustust haiguse varajases staadiumis (Ziegelasch *et al.*, 2017).

Andmed jalgade strukturaalsete ja funktsionaalsete muutuste kohta varase RA korral puuduvad. Kahjuks enamik artriidi aktiivsust hindavaid skaalasid isegi ei hõlma jalaliigeseid, kuigi uuringud on näidanud, et juba varase RA korral võivad esineda nii labakäe kui ka labajala erosiivsed muutused ning seetõttu on soovitav teha kohe diagnoosimisel ka visualiseerivad uuringud labajalgadest (Boutry *et al.*, 2003).

Mitmetes uuringutes on püütud selgitada elustiiliga seotud tegureid reumatoid-artriidi kujunemisel. Toitumis- ja suitsetamisharjumusi on põhjalikult uuritud, kuna need võivad mõjutada keha struktuurimuutusi. Varase reumatoidartriidi kohta on aga andmeid napilt ja tulemused on endiselt ebaselged. Seetõttu on vaja eraldi hinnata käte-jalgade strukturaalseid ja funktsionaalseid muutusi ning markereid, mis võivad nende muutustega seotud olla.

UURIMISTÖÖ EESMÄRGID

Uurimistöö üldine eesmärk on käte ja jalgade strukturaalsete ning funktsionaalsete muutuste esinemise hindamine varase reumatoidartriidi korral ning nende muutustega seostuvate faktorite leidmine.

Uurimistöö spetsiifilised eesmärgid

1. Hinnata, kas juba varase reumatoidartriidi korral esinevad kätel ja jalgadel strukturaalsed ning funktsionaalsed muutused võrreldes kontrollrühmaga ning kas need muutused on kätel ja jalgadel sarnased.
2. Uurida käte ja jalgade strukturaalsete ning funktsionaalsete muutuste vahelist seost põletikumarkeritega.
3. Hinnata, kas käeluude mineraalaine tiheduse muutused on seotud artriidi foonil tekkivate erosioonidega.
4. Leida kliinilisi elustiili markereid, mis võiksid seostuda käeluude mineraalaine tiheduse vähenemise ja erosiivsete muutustega varase reumatoidartriidi korral.
5. Hinnata, kas varase reumatoidartriidi korral tekkivad käte ja jalgade strukturaalsed muutused on seotud selliste elustiili teguritega nagu toitumisharjumused ja suitsetamine.

Uuritavad

Uuringusse kaasati 83 järjestikust Tartu Ülikooli Kliinikumis ajavahemikul jaanuar 2012 – mai 2014 diagnoositud esmase reumatoidartriidi diagnoosiga patsienti, kelle puhul olid täidetud ACR/EULAR 2012. aasta reumatoidartriidi klassifikatsiooni kriteeriumid (Aletaha *et al.*, 2010). Reumatoidartriidi patsientide vaevused polnud kestnud üle ühe aasta.

Rahvastikupõhiseseks kontrollgrupiks moodustati juhuvalim perearsti nimistust (321 uuritavat), kelle vanuseline ja sooline jaotus vastas Eesti rahvastiku 2013. aastal hinnatud struktuurile.

Meetodid

Varase reumatoidartriidi gruppi kuuluvaid patsiente intervjueeriti esmaste haigusnähtude tekke teemal. Hinnati kaasuvate haiguste esinemist, kasutatavate ravimite tarvitamist ning suitsetamise anamneesi. Reumatoidartriidi diagnoos kinnitati elektroonilise haigusloo andmete põhjal ning uuritavad klassifitseeriti ACR/EULAR 2012 RA kriteeriumite alusel.

Läbivaatusel hinnati RA patsientidel turses ja valusate liigeste arv. Kõigil uuritavatel mõõdeti pikkus, kehakaal ning arvutati kehamassiindeks (KMI). RA patsientide artriidi aktiivsus hinnati DAS28 skoori põhjal. Lihasjõudluse hindamiseks kasutati 30 sekundi jooksul toolilt tõusmise ning käe pigistusjõu teste.

Patsiente küsitleti viimase ööpäeva jooksul tarvitatud toidu ja jookide kohta 24 tunni toitumise intervjuu alusel. Andmed sisestati Tervise Arengu Instituudi välja töötatud NutriData programmi, hinnates tarbitud toidust saadud energiasisaldust ja toitainete kogust.

Paastuplasmas määrati CRV ja ESR-i tase ning reumatoidartriidi spetsiifiliste antikehade (anti-CCP ja RF) olemasolu. Vereseerumis mõõdeti vitamiin D3, Ca, OPG, PTH, IL-6, TNFa ja IL-1b tase.

Varase reumatoidartriidi grupi patsientidel uuriti RA spetsiifilise luulise kahjustuse esinemist labakäte röntgenülesvõtetel, hinnates liigespilu kitsenemist ning erosiivsete muutuste esinemist.

Lunar Prodigy DXA luudensitomeetriga mõõdeti mõlemas uuritavate grupis (varane RA ja kontrollgrupp) eraldi käe ja jala luu-, lihas- ning rasvamass. Lisaks mõõdeti kogu keha luumass, luu mineraalaine tihedus käe, reieluu kaela, trohanteri, proksimaalse ning ultradistaalse raadiuse piirkonnas.

Statistiliste analüüside läbiviimiseks kasutati Statistica versiooni 13.3 (Windows) ja SPSS-i versiooni 27.0 (IBM Corp., USA). Kõiki andmeid testiti normaaljaotuvuse suhtes. Normaaljaotuvusega pidevaid tunnuseid esitati keskmise ja standardhälbega. Andmeid, mis ei olnud normaaljaotuvusega, kirjeldati mediaani ja interkvartiilse vahemiku abil. Varase RA patsientide ja kontrollgrupi uuritavate normaaljaotuvusega parameetrite keskmiste võrdlemiseks kasutati Studenti *t*-testi ning mittenormaaljaotuvuse korral mediaanide võrdlemiseks Mann–Whitney *U*-testi. Binaarsete väärtuste ja riskifaktorite vahelisi seoseid analüüsiti logistilise regressioonimudeli abil, pidevate väärtuste ja riskifaktorite vahelisi seoseid uuriti lineaarse regressioonimudeli abil.

Uurimistöö tulemused ja järeldused

Juba varase reumatoidartriidi korral esinevad kätes ja jalgades erinevad struktuursed ning funktsionaalsed muutused.

1. Artriidi diagnoosiga patsientide grupis oli väiksem käte ja jalgade lihasmass ning sellest tingituna ka halvenenud lihasfunktsioon. Varase artriidi esinemine oli seotud nõrgema käte pigistusjõuga ja kehvema lihasjõudlusega 30 sekundi jooksul toolilt tõusmise testil. Lisaks oli neil suurem käte rasvamass, samas olulist muutust jalgade rasvamassis ei esinenud. Käte ega jalgade luumass ei olnud varase artriidi korral oluliselt vähenenud, samas võrreldes kontrollgrupiga esines neil juba oluline käeluude mineraalaine tiheduse vähenemine.
2. Varase artriidi korral oli käte ja jalgade lihasmassi vähenemine seotud kõrgema CRV väärtusega, viidates RA korral esinevale süsteemsele põletikulisele kahjustusele.

3. Varase RA korral tekkivad erosioonid ei seostu käeluude mineraalaine tiheduse vähenemisega, ehkki 76%-l varase RA-ga patsientidest esinesid erosioonid haiguse algfaasis.
4. Käeluude mineraalaine tiheduse vähenemise ja erosiivsete muutuste tekkega seostuvad faktorid erinevad reumatoidartriidi varases faasis. Käeluude mineraalaine tiheduse vähenemine seostus kõrgema IL-6 taseme ning reumatoidfaktori positiivsusega. Samas elustiilifaktorid, nagu kõrgem KMI ja suitsetamine, seostusid suurenenud erosiivsete muutuste tekke tõenäosusega labakäe röntgenülesvõtetel. Suitsetamine tõstis erosiivsete muutuste tekke riski 10 korda.
5. Varase artriidiga patsientide dieedi ning käte ja jalgade strukturaalsete muutuste tekke vahel enamasti olulisi seoseid polnud. Ainult kõrgem polüküllastumata rasvhapete (PUFA) kogus toidus seostus käte väiksema rasvamassiga. Käte ega jalgade lihasmassi muutustele ei omanud mõju toiduga tarvitatud PUFA ega valkude hulk. Suitsetamisel ei olnud varase RA korral olulist mõju ei käte ega ka jalgade luu- ning lihasmassile, niisamuti mitte lihasfunktsiooni muutustele.

Uurimus aitas selgitada mõningaid faktoreid, mis seostuvad varase reumatoidartriidi korral tekkivate käte ja jalgade strukturaalsete muutustega. Juba RA varases faasis esinevad nii strukturaalsed kui ka funktsionaalsed käte ja jalgade muutused. Esmased nähud võivad olla käeluude mineraalaine tiheduse vähenemine, sümmeetriline käte ja jalgade lihasmassi vähenemine ning käte rasvamassi suurenemine. Seepärast on varase reumatoidartriidi korral oluline hinnata käsi ja jalgu paralleelselt, kuna artriidist mõjutatud liigeste haaratus võib patsientidel erineda. Uuringu tulemusena leidsime ka, et madalam käeluude mineraalaine tihedus seostus madalama seerumi 25 (OH) D-vitamiini tasemega.

Praktilisest aspektist võiks varase RA korral lisaks tavapärasele röntgenuuringule teostada käeluude mineraalaine tiheduse ning lihasmassi mõõtmise koos seerumist IL-6 määramisega. Meetod võimaldaks paremini profileerida varase reumatoidartriidi patsiente, valimaks neile paremad ning terviklikumad ravistrateegiad. Lisaks võiks osteoprotegeriini määramine seerumist olla täiendav diagnostiline marker põletikulise aktiivsuse ning aktiivse liigeskahjustuse hindamiseks reumatoidartriidi korral.

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13. PUBLICATIONS

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Professional employment:

01.07.2012–31.08.2012	University of Tartu, Faculty of Medicine, Department of Internal Medicine, specialist
01.09.2012–	Tartu University Hospital, Department of Internal Medicine, rheumatologist
2012–2014	East Viru Central Hospital, rheumatologist
01.10.2013–28.02.2015	University of Tartu, Faculty of Medicine, Department of Internal Medicine, specialist
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2019–2023	Viljandi County Hospital, rheumatologist
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Professional associations:

2008–	Estonian Society for Rheumatology
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Scientific work:

My research mainly focuses on hand and leg structural and functional changes, as well as on factors that associate with these alterations in early rheumatoid arthritis.

Publications in international peer-reviewed journals:

1. **Valner A**, Müller R, Kull M, Põlluste K, Lember M, Kallikorm R. Does dietary polyunsaturated fatty acid intake associate with bone mineral density and limb structural changes in early rheumatoid arthritis? Nutrition and Metabolic Insights. 2023;16:11786388231176169.
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Erialane kuuluvus:

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Teadustegevus:

Minu teadustöö keskendub käte ja jalgade strukturaalsete ja funktsionaalsete muutuste ning nende muutuste tekkega seonduvate faktorite hindamisele varase reumatoidartriidi korral.

Artiklid rahvusvahelistes eelretsenseeritavates ajakirjades:

1. **Valner A**, Müller R, Kull M, Põlluste K, Lember M, Kallikorm R. Does dietary polyunsaturated fatty acid intake associate with bone mineral density and limb structural changes in early rheumatoid arthritis? Nutrition and Metabolic Insights. 2023;16:11786388231176169.
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