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METABOLIC AND INFLAMMATORY FACTORS IN UPPER EXTREMITYS SOFT-TISSUE DISORDERS

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But where can wisdom be found?
And where is the place of understanding?
Job 28:12

SUMMARY

Upper extremity soft-tissue disorders (UESTDs) are common painful conditions relating to tendons and their adjacent structures. The etiology of UESTDs, particularly the role of metabolic and inflammatory factors, is unknown. Some studies have found associations between obesity and diabetes with UESTDs. To date, few studies have assessed the role of cytokines in UESTDs and virtually nothing is known about the role of adipokines in these disorders. Animal experiments as well as studies conducted with human tissue samples have found evidence of inflammation in tendons, suggesting that pro-inflammatory cytokines play a role in UESTDs. The expressions of pro-inflammatory cytokines and adipokines in serum are altered in obesity, however it is unclear whether these compounds contribute to the symptoms experienced by UESTD patients.

The overall aim of this study was to explore the role of metabolic and inflammatory factors in shoulder pain and UESTDs. This study utilized the Health 2000 Survey, a health examination of a representative sample of the Finnish general population conducted by the National Institute of Health and Welfare (N = 6354). In addition, a sample of actively working patients with incipient UESTDs (N = 163) and a healthy control group (N = 42) were examined in the Finnish Institute of Occupational Health.

In a representative sample of the general population, the prevalence of shoulder joint pain in the past month was 16% and that of possible or probable chronic rotator cuff tendinitis was 3%. Every third patient with incipient UESTDs, reported full or substantial recovery within three months. Body mass index, waist circumference and type 2 diabetes were associated with shoulder joint pain, whereas waist circumference was associated with chronic rotator cuff tendinitis. Moreover, waist circumference, low levels of HDL cholesterol, high levels of triglycerides and high levels of an adipokine, visfatin, were associated with the intensity of upper extremity pain in patients with incipient UESTDs. Serum levels of soluble interleukin 1 receptor 2 and soluble ST2 receptor were higher and those of interleukin 18 lower in patients with incipient UESTDs compared with the healthy controls. Furthermore, high levels of two adipokines, resistin and visfatin, predicted a higher recovery rate from UESTDs.

The study findings suggest that obesity and diabetes are associated with upper extremity pain and chronic rotator cuff tendinitis. The underlying mechanisms are largely unknown, however the increased expression of pro-inflammatory cytokines in obesity may modify pain sensitivity and promote inflammation in tendon and its adjacent structures. In diabetes, the precipitation of advanced glycation end products in tendons is thought to increase the tissue's susceptibility to tendon disorders.

Furthermore, the findings point towards an independent role of interleukin 1 family biomarkers in UESTDs. Therefore, incipient UESTDs may promote inflammatory activity, potentially altering serum biomarker levels. Finally, adipokines are recognized to exert a role in inflammation; the findings of this study suggest that they may play a role as modifiers of upper extremity pain intensity and also in the recovery from UESTDs.

YHTEENVETO

Yläraajan jänteisiin ja niitä ympäröiviin kudoksiin paikantuvat sairaudet eli yläraajan pehmytkudossairaudet ovat yleinen yläraajakivun aiheuttaja väestössä. Näiden sairauksien syitä ja syntymekanismeja ei tunneta tarkkaan. Eräissä tutkimuksissa lihavuus ja diabetes ovat olleet yhteydessä yläraajan jännesairauksien esiintyvyyteen. Tulehdusvälittäjäaineiden eli sytokiinien merkitystä yläraajan pehmytkudossairauksissa on tutkittu vähän ja mm. rasvakudoksen erittämien adipokiinien merkitystä niissä ei ole tutkittu lainkaan. Koe-eläimiltä ja potilailta saatujen kudosnäytteiden jännerakenteista on löydetty merkkejä tulehduksesta, minkä perusteella sytokiinien on ajateltu liittyvän yläraajan pehmytkudossairauksien kehittymiseen. Lihavuus aiheuttaa sekä sytokiinien että adipokiinien pitoisuuksien muutoksia veressä. Näiden veressä esiintyvien merkkiaineiden yhteys yläraajan pehmytkudossairauksiin on kuitenkin vielä selvittämättä.

Tämän tutkimuksen tavoitteena oli tarkastella aineenvaihdunta- ja tulehdustekijöiden yhteyttä olkapääkipuun ja yläraajan pehmytkudossairauksiin. Olkapään sairauksia selvittävään tutkimukseen valittiin suomalaista väestöä edustavaan Terveyden ja hyvinvoinnin laitoksen Terveys 2000 -tutkimukseen osallistuneet työikäiset henkilöt (N=6354). Yläraajan pehmytkudossairauksia selvitettiin Työterveyslaitoksen yläraajaprojektissa työterveyshuoltoon yläraajakivun vuoksi hakeutuneilla työntekijöillä (N=163). Heille valittiin yläraajasairauksien suhteen terveistä henkilöistä koostuva kontrolliryhmä (N=42). Terveys 2000 -tutkimukseen osallistuneet ja työterveyshuoltoon hakeutuneet henkilöt tutkittiin kliinisesti. Kaikilta tutkittavilta mitattiin pituus, paino ja vyötärönympärys sekä otettiin verinäyte aineenvaihdunta- ja tulehdustekijöiden määrittämistä varten.

Olkapääkipua oli viimeksi kuluneiden 30 päivän aikana ollut 16 % :lla suomalaisista työikäisistä. Krooninen kiertäjäkalvosimen oireyhtymä todettiin kliinisessä tutkimuksessa 3 %:lla. Työterveyshuollon potilasaineistossa merkittävimmät diagnoosiryhmät olivat kiertäjäkalvosimen tendinopatia ja kyynärpään sivunastatulehdus, joita kumpaakin oli noin kolmannes tapauksista. Viidenneksellä oli kipua ilman spesifistä diagnoosia. Kolmannes potilaista toipui joko olennaisesti tai kokonaan kolmessa kuukaudessa.

Painoindeksi, vyötärönympärys ja tyypin 2 diabetes olivat väestöaineistossa yhteydessä olkapääkivun esiintyvyyteen. Vyötärönympärys oli yhteydessä myös kroonisen kiertäjäkalvosinoireyhtymän esiintyvyyteen. Vyötärönympärys, matala HDL-kolesteroli, kohonneet triglyseridit ja adipokiini visfatiinin korkea pitoisuus seerumissa olivat yhteydessä yläraajakipuun yläraajapotilailla. Seerumin liukoisen interleukiini 1 -reseptori 2:n sekä ST2-reseptorin pitoisuudet olivat merkittävästi korkeampia yläraajapotilailla verrattuna terveisiin kontrollihenkilöihin. Lisäksi adipokiinien resistiini ja visfatiini korkeat pitoisuudet olivat yhteydessä yläraajapotilaiden parempaa toipumisennusteeseen.

Tutkimustulosten perusteella lihavuudella ja diabeteksella on yhteys olkapääkipuun ja krooniseen kiertäjäkalvosimen oireyhtymään. Yhteyden taustalla olevia mekanismeja ei tunneta hyvin. Lihavuuteen liittyen veressä kiertävät sytokiinit voivat herkistää kivulle ja ylläpitää tulehdusta jännerakenteissa. Diabeetikoilla glykosylaation seurauksena jänteisiin kertyvien aineenvaihduntatuotteiden ajatellaan aiheuttavan jännetulehduksia.

Potilasaineistolla interleukiini 1 -perheen merkkiaineilla oli riippumaton yhteys yläraajan pehmytkudossairauksiin. Löydöksen perusteella yläraajan pehmytkudossairauksiin voisi alkuvaiheessa liittyä tulehdusta, joka muuttaa seerumin merkkiainepitoisuuksia. Myös adipokiinien tiedetään liittyvän tulehdukseen. Tutkimuksen havainnot viittaavat siihen, että adipokiineilla saattaa olla vaikutusta yläraajakipuun sekä yläraajan pehmytkudossairauksista toipumiseen.

CONTENTS

ABBREVIATIONS

AGE	Advanced glycation end product
BMI	body mass index
CI	confidence interval
COX2	cyclooxygenase 2
CRP	C-reactive protein
GEE	generalized estimating equation
HDL	high density lipoprotein
IL-1	interleukin 1 (6, 8, 18, 21, 33)
IL1-Ra	interleukin 1 receptor antagonist
OR	odds ratio
PGE2	prostaglandin E2
SD	standard deviation
sIL-1RII	soluble interleukin 1 receptor 2
TGFβ	transforming growth factor beta
Th2	T helper 2
TNFα	tumor necrosis factor alpha
UESTD	upper extremity soft tissue disorder

PUBLICATIONS

I Lifestyle and metabolic factors in relation to shoulder pain and rotator cuff tendinitis: a population-based study. Rechardt M, Shiri R, Karppinen J, Jula A, Heliövaara M, Viikari-Juntura E. BMC Musculoskelet Disord. 2010 Jul 20;11:165.

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1 INTRODUCTION

Upper extremity soft-tissue disorders (UESTDs) are tendon-related painful conditions, distinguishable from nerve entrapments and osteoarthritis. They are prevalent, frequently associated with work disability and some of them may result in high healthcare costs (Silverstein, Viikari-Juntura et al. 2002, Huisstede, Bierma-Zeinstra et al. 2006, Lipscomb, Schoenfisch et al. 2015). Between 20% and 40% of the working population report that they have experienced upper limb pain during the preceding year (Huisstede, Bierma-Zeinstra et al. 2006). In a national survey, one out of every ten Canadians aged 20 or older stated that they had suffered an upper extremity disorder during the preceding one year that was serious enough to limit their normal activities (IWH 2005). In Washington State between 1990 and 1998, upper extremity disorders resulted in $2.6 billion in direct costs and 20.5 million lost workdays (Silverstein, Viikari-Juntura et al. 2002). The European Agency for Safety and Health at Work has estimated that all costs due to work related neck and upper limb musculoskeletal disorders in the Nordic countries and the Netherlands ranged between 0.5% and 2% of the Gross National Product (Buckle and Devereux 1999). In 2013, 10% of all cases of occupational disease-related insurance compensation claims were attributable to UESTDs in Finland (FIOH 2015). According to the statistics of the Social Insurance Institution of Finland, soft-tissue disorders of the shoulder were the most commonly compensated group of UESTDs in 2014 and constituted 4.4% of all compensated sickness absence days, averaging 44 workdays per individual per year and totalling €41 million (SIIF 2014).

The etiology of UESTDs is only partly understood but there is one clear fact UESTDs are more likely to affect older individuals. Age is linearly associated with shoulder disorders, however the highest risk of epicondylitis is seen in individuals between 40 and 50 years (Shiri, Viikari-Juntura et al. 2006). All UESTDs are more prevalent in women compared to men (Treaster and Burr 2004). Physical load factors increase the risk of all UESTDs (Leclerc, Landre et al. 2001, Roquelaure, Ha et al. 2009, van Rijn, Huisstede et al. 2010).

Obesity has been suggested to be associated with clinically defined UESTDs (Gaida, Ashe et al. 2009). Moreover, a few studies have found an association between obesity and non-specific shoulder pain (Evanoff, Sabbath et al. 2014, Kim, Suh et al. 2015). There may be other metabolic factors, for example, diabetes has been suggested as a risk factor for rotator cuff tendinopathy and trigger finger tenosynovitis (Abate, Schiavone et al. 2013, Lin, Lin et al. 2015)

The tendon and its adjacent structures show inflammation in UESTDs. Moreover, obesity increases the expression of adipokines and pro-inflammatory cytokines. Accordingly, adipokines and cytokines might be components of an inflammatory process and possibly be considered as biomarkers for UESTDs. To date, there is only anecdotal information on the associations of adipokines and cytokines with UESTDs.

This study aims to explore the role of metabolic and inflammatory factors in clinically defined UESTDs and non-specific upper limb pain.

2 REVIEW OF THE LITERATURE

2.1 DEFINITION OF UPPER EXTREMITY DISORDERS

Upper extremity disorders include osteoarthritis in the joints, soft-tissue disorders of the tendon structures, peripheral nerve entrapment and different sequelae after accidental injuries. Upper extremity soft-tissue disorders (UESTDs) are a group of tendon related conditions emerging as a result of pathological alterations of the tendon matrix, peritendon, tenosynovium or bursas or tendon insertions producing pain in the site of the disorder, i.e. shoulder, elbow, forearm, wrist or hand. Identification of specific UESTDs such as rotator cuff tendinitis, lateral and medial epicondylitis as well as De Quervain's tenosynovitis requires the fulfilment of predetermined criteria during the clinical examination (Sluiter, Rest et al. 2001).

Rotator cuff tendinopathy: The structures involved in rotator cuff tendinopathy include the supraspinatus, the infraspinatus and subscapular tendons as well as the tendon of the long head of the biceps. Clinical signs of rotator cuff tendinopathy are pain upon resisted shoulder abduction, external or internal rotation, resisted elbow flexion and painful arc on active upper arm elevation (Sluiter, Rest et al. 2001).

Epicondylitis: Lateral and medial epicondylitis are characterized by activity related pain in the muscle-tendon junction or at the insertion of wrist extensor (lateral) or flexor (medial) muscles at the epicondyle (Sluiter, Rest et al. 2001). The clinical signs of epicondylitis include tenderness on palpation of the epicondyle and local pain on resisted wrist extension (lateral) or wrist flexion (medial).

Peritendinitis and tenosynovitis of the forearm and wrist region: Peritendinitis and tenosynovitis of the forearm and wrist region are characterized by recurrent pain on the movement of the wrist and finger extensors or flexors. The clinical findings include symptom provocation during resisted movement of the muscles and pain on palpation of the affected tendons. There may also be palpable crepitus and swelling of wrist or forearm dorsum (Sluiter, Rest et al. 2001). De Quervain's disease is a stenosing tenosynovitis of the long abductor and short extensor tendons of the thumb. It is identified by the presence of pain over the radial side of the wrist and a positive Finkelstein's test, or pain on resisted thumb extension or abduction.

Non-specific upper extremity pain: Non-specific upper extremity pain can be localized in the muscles, tendons or around the joints but the criteria of specific upper extremity disorders are not fulfilled.

2.2 PREVALENCE AND INCIDENCE OF UPPER EXTREMITY MUSCULOSKELETAL DISORDERS

2.2.1 PREVALENCE

Upper extremity pain

In the general population, the prevalence of shoulder pain during the preceding month ranges from 11% to 30% (Luime, Koes et al. 2004, Miranda, Viikari-Juntura et al. 2005, Gill, Shanahan et al. 2013, Davatchi, Sandoughi et al. 2015), elbow pain from 7% to 14% (Urwin, Symmons et al. 1998, Sim, Lacey et al. 2006, Walker-Bone, Palmer et al. 2012, Hegmann, Thiese et al. 2014, Davatchi, Sandoughi et al. 2015) and forearm pain from 8% to 15% (Macfarlane, Hunt et al. 2000, Sim, Lacey et al. 2006, Davatchi, Sandoughi et al. 2015). In the working population, the prevalence of shoulder pain during the preceding month ranges between 16% and 63% (Pandy 2013, Hegmann, Thiese et al. 2014, Nordander, Hansson et al. 2016), with elbow pain being less common, experienced by between 5% and 12% of the working population (Palmer, Cooper et al. 2001, Herquelot, Bodin et al. 2013, Hegmann, Thiese et al. 2014). Moreover, one out of every three members of the general working population reports that he/she has suffered some form of upper extremity pain during the preceding month (Roquelaure, Ha et al. 2006, Sim, Lacey et al. 2006) and every fifth has experienced sufficient chronic pain to limit their daily activities (Gummesson, Atroshi et al. 2003).

Upper extremity disorder

In the general population, the prevalence of shoulder tendinopathy ranges between 2.5% and 7.4% (Walker-Bone, Palmer et al. 2004, Shiri, Varonen et al. 2007, Roquelaure, Ha et al. 2009, Davatchi, Sandoughi et al. 2015), lateral epicondylitis between 0.7% and 3.0% (Linaker, Walker-Bone et al. 1999, Shiri, Varonen et al. 2007, Shiri and Viikari-Juntura 2011, Walker-Bone, Palmer et al. 2012, Davatchi, Sandoughi et al. 2015), medial epicondylitis between 0.3% and 1.0% (Shiri, Varonen et al. 2007, Shiri and Viikari-Juntura 2011, Walker-Bone, Palmer et al. 2012, Davatchi, Sandoughi et al. 2015), de Quervain's disease between 0.2% and 1.2% (Walker-Bone, Palmer et al. 2004, Roquelaure, Ha et al. 2009, Davatchi, Sandoughi et al.

2015) and tenosynovitis of the hand or wrist between 0.8% and 1.7% (Walker-Bone, Palmer et al. 2004, Roquelaure, Ha et al. 2009). In the working population, the prevalence of shoulder tendinopathy ranges between 6% and 30% (Bodin, Ha et al. 2012, Bugajska, Zolnierczyk-Zreda et al. 2013, Hegmann, Thiese et al. 2014, da Costa, Baptista et al. 2015, Nordander, Hansson et al. 2016, Stucchi, Battevi et al. 2016), lateral epicondylitis between 1% and 8% (Bugajska, Zolnierczyk-Zreda et al. 2013, Pullopdissakul, Ekpanyaskul et al. 2013, Gerr, Fethke et al. 2014, Hegmann, Thiese et al. 2014, Meroni, Scelsi et al. 2014, Stucchi, Battevi et al. 2016), medial epicondylitis between 1% and 5%, and tendinopathy of the wrist and hand between 4% and 20% (Ono, Nakamura et al. 1998, Descatha, Leclerc et al. 2003, Gold, d'Errico et al. 2009, Bugajska, Zolnierczyk-Zreda et al. 2013, Pullopdissakul, Ekpanyaskul et al. 2013, Gerr, Fethke et al. 2014, Stucchi, Battevi et al. 2016).

2.2.2 INCIDENCE

Upper extremity pain

The annual incidence of shoulder pain ranges between 7% and 15% (Miranda, Viikari-Juntura et al. 2001, Bot, van der Waal et al. 2005, Ostergren, Hanson et al. 2005, Greving, Dorrestijn et al. 2012, Herin, Vézina et al. 2012, Lamy, Descatha et al. 2014) and arm or forearm pain between 4% and 21% (Macfarlane, Hunt et al. 2000, Bot, van der Waal et al. 2005, Palmer, Reading et al. 2008). In general practice populations, the annual incidence of the first consultation has been reported to be between 0.3% and 1.1% for shoulder pain (Linaker, Walker-Bone et al. 1999, Bot, van der Waal et al. 2005, Greving, Dorrestijn et al. 2012, Tekavec, Jöud et al. 2012).

Upper extremity disorders

In the general population, the annual incidence of shoulder disorders ranges between 0.1% and 1.3% (Linaker, Walker-Bone et al. 1999, Bot, van der Waal et al. 2005, Shiue, Lu et al. 2008, Chung, Hung et al. 2013); for lateral epicondylitis, it is between 0.25% and 0.45% (Sanders, Maradit Kremers et al. 2015). In general practice populations, the annual incidence of consultations for a shoulder disorder has been reported to range from 0.7% to 1.5%, with the corresponding range for lateral epicondylitis being 0.3% to 1.1% (Linaker, Walker-Bone et al. 1999, Bot, van der Waal et al. 2005, Linsell, Dawson et al. 2006, Shiri and Viikari-Juntura 2011). In the working populations, the annual incidence of shoulder disorders ranges from 0.5% to

9.4% (Roquelaure, Mariel et al. 2002, Linsell, Dawson et al. 2006, Shiue, Lu et al. 2008, Bodin, Ha et al. 2012, Chung, Hung et al. 2013, Gerr, Fethke et al. 2014), lateral epicondylitis from 0.4% to 2.1%, medial epicondylitis from 0.1% to 1.5% (Roquelaure, Mariel et al. 2002, Descatha, Leclerc et al. 2003, Shiue, Lu et al. 2008, Wolf, Mountcastle et al. 2010, Chung, Hung et al. 2013, Descatha, Dale et al. 2013), wrist/hand soft-tissue disorders from 2.2% to 3.1% (Roquelaure, Mariel et al. 2002, Werner, Franzblau et al. 2005), and de Quervain's disease from 0.1% to 0.3% (Shiue, Lu et al. 2008, Wolf, Sturdivant et al. 2009, Chung, Hung et al. 2013). In working populations performing manually intensive tasks, the annual incidence of lateral epicondylitis ranges between 2% and 6.2%, medial epicondylitis between 1.5% and 1.8% (Shiri and Viikari-Juntura 2011, Fan, Silverstein et al. 2014, Gerr, Fethke et al. 2014), and that of de Quervain's disease or wrist tendinitis between 1.9% and 5.4% (Leclerc, Landre et al. 2001, Harris, Eisen et al. 2011, Gerr, Fethke et al. 2014, Harris-Adamson, You et al. 2014).

In addition to the high prevalence and incidence of upper extremity musculoskeletal pain and disorders, the large number of healthcare consultations and compensation claims attributable to these conditions highlights the ubiquitous nature of upper extremity musculoskeletal related health problems all around the world (Huisstede, Bierma-Zeinstra et al. 2006, Van Eerd, Munhall et al. 2016). Upper extremity musculoskeletal pain and disorders are more prevalent in the working population than in the general population. In particular, workers in certain occupations are at increased risk of suffering upper extremity musculoskeletal pain and disorders owing to their exposure to physical and psychosocial risk factors (Liaker and Walker-Bone 2015). Unfortunately, in a large proportion of the studies conducted in occupational populations, a representative sample of working population was not recruited, and their sample populations have been small. Moreover, the studies have often applied various case definitions for upper extremity musculoskeletal disorders.

2.3 RISK FACTORS FOR UESTDS

2.3.1 BIOLOGICAL FACTORS

2.3.1.1 Sex

Upper extremity pain

In general, women report upper extremity pain (Palmer, Cooper et al. 2001, Sundstrup, Jakobsen et al. 2014, Cho, Cho et al. 2015, Park, Kim et al. 2015, Soe, Laosee et al. 2015, Alavi, Makarem et al. 2016) and shoulder pain

(Silverstein, Fan et al. 2009, Smith, Silverstein et al. 2009, Gill, Shanahan et al. 2013) more commonly than men. However, some studies have found no sex-related differences in the prevalence of pain in the elbow (Roquelaure, Ha et al. 2006, Soe, Laosee et al. 2015, Thetkathuek, Meepradit et al. 2016), or a higher prevalence or incidence of elbow pain in men than in women (Palmer, Cooper et al. 2001, Bot, van der Waal et al. 2005).

Upper extremity disorder

Sex is a well-known risk factor for carpal tunnel syndrome. Previous studies found that women show a 2- to 3-fold higher prevalence and incidence of carpal tunnel syndrome than men (Atroshi, Gummesson et al. 2007, Bongers, Schellevis et al. 2007, Luckhaupt, Dahlhamer et al. 2013, Petit, Ha et al. 2015).

Women have also other UESTDs more frequently than men (Treaster and Burr 2004, Fan, Silverstein et al. 2009, Kiani, Goharifar et al. 2014). The prevalence and incidence of many UESTDs are higher in women than in men e.g. rotator cuff disorders (Walker-Bone, Palmer et al. 2004, Bot, van der Waal et al. 2005, Roquelaure, Ha et al. 2009, Bodin, Ha et al. 2012, Stucchi, Battevi et al. 2016), lateral epicondylitis (Leclerc, Landre et al. 2001, Shiri, Viikari-Juntura et al. 2006, Roquelaure, Ha et al. 2009, Walker-Bone, Palmer et al. 2012, Descatha, Dale et al. 2013, Fan, Silverstein et al. 2014, Sanders, Maradit Kremers et al. 2015, Stucchi, Battevi et al. 2016), medial epicondylitis (Walker-Bone, Palmer et al. 2004, Shiri, Viikari-Juntura et al. 2006, Walker-Bone, Palmer et al. 2012), and wrist tendinitis or de Quervain's disease (Walker-Bone, Palmer et al. 2004, Wolf, Sturdivant et al. 2009, Harris, Eisen et al. 2011).

Overall, women are at a higher risk of experiencing upper extremity pain and disorders than men. The differences between the sexes can be due to several factors, for example pain sensitivity may differ between men and women (Mapplebeck, Beggs et al. 2016). In addition to a sex difference in hormonal effects in the upper extremity (Toesca, Pagnotta et al. 2008), women may also respond differently to physical and psychosocial stressors in their daily activities and work-life (Hooftman, van Poppel et al. 2004, Wijnhoven, de Vet et al. 2006). Although, the sex differences can partly be due to confounding factors there is one report claiming that they do not disappear after adjustment for known confounding factors (Treaster and Burr 2004). The differences in exposure to physical and psychosocial factors between men and women seem to play only a small role in the sex difference in the risk of upper extremity disorders (de Zwart, Frings-Dresen et al. 2001, Hooftman, van Poppel et al. 2004, Hooftman, van der Beek et al. 2009).

2.3.1.2 Age

Age is commonly associated with upper extremity pain and disorders. In general, the occurrence of upper extremity pain and disorders increases with age. The prevalence of chronic upper extremity pain (Gummesson, Atroshi et al. 2003, Herin, Vezina et al. 2014, Meroni, Scelsi et al. 2014, Pelissier, Fontana et al. 2014, Zoer, Frings-Dresen et al. 2014, Kaliniene, Ustinaviciene et al. 2016), persistent upper extremity pain (Palmer, Reading et al. 2008), and shoulder pain (Miranda, Viikari-Juntura et al. 2001, Bot, van der Waal et al. 2005) increases with age, particularly after the age of 40-45 years.

In the general population, the prevalence of upper extremity disorders increases noticeably after the age of 45 years (Walker-Bone, Palmer et al. 2004, Salaffi, De Angelis et al. 2005, White, Titchener et al. 2014), while in the working population, the risk increases after the age of 30 years (Roquelaure, Ha et al. 2009). Moreover, the risk of shoulder disorders increases after the age of 40 years (Roquelaure, Ha et al. 2006, Bodin, Ha et al. 2012, Stucchi, Battevi et al. 2016) and is highest between 40 and 64 years (Bot, van der Waal et al. 2005, Greving, Dorrestijn et al. 2012, White, Titchener et al. 2014). A linear relationship has been observed between age and the prevalence of shoulder tendinopathy (Walker-Bone, Palmer et al. 2004, Lin, Lin et al. 2015, Sansone, Meroni et al. 2015), suggesting that there may be a gradual degeneration of the rotator cuff with age and also highlighting the chronic nature of rotator cuff tendinopathy (Teunis, Lubberts et al. 2014). Moreover, in a study of arthroscopic rotator cuff repair, rotator cuff tendons were more severely injured in subjects over 60 years of age compared with the younger patients, pointing to a significant effect of age on the condition of the shoulder tendons (Djerbi, Chammas et al. 2015). Similarly, after the age of 35-40 years, the prevalence of lateral epicondylitis and wrist tendinopathy increases noticeably (Roquelaure, Ha et al. 2006, Stucchi, Battevi et al. 2016). The incidence of lateral epicondylitis peaks between ages 40 and 60, levelling off at older ages (Shiri and Viikari-Juntura 2011, Herquelot, Guéguen et al. 2013, Fan, Silverstein et al. 2014, Sanders, Maradit Kremers et al. 2015). In some working populations, however, younger workers may have a disproportionally higher risk of experiencing distal upper extremity disorders, such as wrist tendinopathy, compared with their older colleagues (Dale, Ryan et al. 2015).

Several age-related changes including degenerative changes, impaired blood circulation, alterations of metabolism, prolonged healing process, slower resolution of hyperalgesia after traumatic injury, and decreased pain tolerance (Gibson and Farrell 2004) may all play roles in upper extremity pain and disorders. Moreover, inflammatory activity mediated by the

interleukin 1 family has been linked to the effects of aging (Dinarello 2006) on upper extremity pain and disorders. Exposure to occupational factors may also potentiate the effects of ageing on UESTDs.

2.3.2 PHYSICAL AND PSYCHOSOCIAL FACTORS AT WORK

2.3.2.1 Physical factors at work

Already in 2004, Punnett and Wegman concluded that there was enough evidence from epidemiological and experimental studies to support a causal role of physical risk factors at work, such as high force demands and repetitive work, and especially their combination, in upper extremity disorders (Punnett and Wegman 2004). Since then, some studies have revealed that UESTDs are more common in the dominant in comparison with the non-dominant hand (Shiri, Varonen et al. 2007, Fan, Silverstein et al. 2014), further supporting the hypothesis that physical loads play a role in the etiology of UESTDs. More recent reviews (van Rijn, Huisstede et al. 2010, Mayer, Kraus et al. 2012) have suggested that heavy lifting, forceful manual exertion, repetitive movements, working with hands above shoulder level and the use of vibrating hand tools are all associated with shoulder pain and disorders.

Physical load factors which have been linked with epicondylitis include forceful activities, forearm pronation, high force combined with high repetition or awkward postures of the wrist (Shiri and Viikari-Juntura 2011, Bodin, Ha et al. 2012, Descatha, Dale et al. 2013, Fan, Silverstein et al. 2014). Wrist bending, high force, twisting, and pinch gripping are tasks considered to increase the risk of tendon disorders in the wrist (Harris, Eisen et al. 2011, Petit Le Manac'h, Roquelaure et al. 2011, Pullopdissakul, Ekpanyaskul et al. 2013).

Some studies among manufacturing workers, for instance, have not detected an association between repetition, high force or awkward postures and lateral epicondylitis (Pullopdissakul, Ekpanyaskul et al. 2013) or between wrist bending and heavy gripping and wrist tendinopathy (Harris-Adamson, You et al. 2014). Surprisingly, one study found evidence that combined wrist extension and heavy power grip conferred protection against wrist tendinopathy (Harris-Adamson, You et al. 2014). However, a recent meta-analysis of five prospective cohort studies stated that combined biomechanical exposure involving the wrist and/or elbow increased the incidence of lateral epicondylitis by 2.6 fold (95% CI 1.9-3.5)(Descatha, Albo et al. 2016).

In conclusion, most studies have found an association between physical load factors at work and UESTDs. Research results regarding some physical exposures and some upper extremity disorders are not in full agreement; this may be due to differences in the methods of assessing physical exposures as well as the excessively small and selected populations examined in some of the studies. Overall, the literature points to a strong and causal relationship between physical work load factors and UESTDs. Therefore, physical work load factors need to be taken into consideration in epidemiological studies on UESTDs.

2.3.2.2 Psychosocial factors at work

The role of psychosocial factors at work in UESTDs is unclear (Bongers, Ijmker et al. 2006). The job demand-control-support model (Karasek, Brisson et al. 1998, Bongers, Ijmker et al. 2006, Park and Jang 2010) has been most often tested. When one considers the work related psychosocial factors, then high job demands, low job control, poor co-worker or supervisor support, low job satisfaction and low job security have all been found to be associated with UESTDs (Werner, Franzblau et al. 2005, van Rijn, Huisstede et al. 2010, Shiri and Viikari-Juntura 2011, Gerr, Fethke et al. 2014). However, some of the study results have been inconsistent (Bongers, Ijmker et al. 2006, van Rijn, Huisstede et al. 2009, van Rijn, Huisstede et al. 2010) and some have had limited statistical power (Haahr and Andersen 2003, Fan, Silverstein et al. 2009, Gerr, Fethke et al. 2014). Moreover, cohort studies have shown no or only modest effects of psychosocial factors on upper extremity disorders (Bongers, Ijmker et al. 2006, Bugajska, Zołnierczyk-Zreda et al. 2013). A review of longitudinal studies of neck and shoulder symptoms, suggested an association between job demand-control-support model variables, such as low control and high job strain and shoulder pain (Kraatz, Lang et al. 2013).

In summary, studies on the role of work related psychosocial factors in upper extremity pain or disorders have reported inconsistent results. Psychosocial factors should be taken into consideration in epidemiological studies on upper extremity disorders, especially in studies investigating non-specific upper extremity pain.

2.3.3 LIFESTYLE AND METABOLIC FACTORS IN UESTDS

2.3.3.1 Obesity

Overall, 11% of the world's men and 15% of its women were obese in 2014 (NCD-RisC 2016). Obesity has been linked with a large number of health problems (Collaborators 2016). The role of obesity is well-known in carpal tunnel syndrome (Shiri, Pourmemari et al. 2015), however, its effect on other UESTDs is uncertain.

In addition to its role as an energy storage site, adipose tissue functions as an organ that produces a range of biologically active mediators inducing a state of systemic chronic low grade inflammation in obese individuals. An earlier systematic review found an association between BMI and incident shoulder pain (Viikari-Juntura, Shiri et al. 2008). This was later supported by a longitudinal working population study, where high BMI values predicted incident severe shoulder pain (Descatha, Teysseyre et al. 2012). Furthermore, high BMI and excessive body fat per cent have been postulated to play a role in rotator cuff tear (Wendelboe, Hegmann et al. 2004, Gumina, Candela et al. 2014, Djerbi, Chammas et al. 2015). There are two cross-sectional studies which detected associations between the BMI value and elbow and wrist pain (Pelissier, Fontana et al 2014, Kin, Suh et al. 2015). Moreover, several reports found evidence that overweight or obesity may be related with upper extremity tendinopathy (Werner, Franzblau et al. 2005) or wrist tendinitis (Leclerc, Landre et al. 2001, Stucchi, Battevi et al. 2016). A general population study detected an association between an increased waist hip ratio and medial epicondylitis in women (Shiri, Viikari-Juntura et al. 2006), whereas a working population study only found evidence of a possible higher risk of UESTDs in obese men (Roquelaure, Ha et al. 2009).

Several studies, however, do not support any role for overweight or obesity in upper extremity pain or disorders. Some investigators did not detect any association between the BMI value and the prevalence of shoulder, elbow or wrist pain (Bodin, Ha et al. 2012, Pelissier, Fontana et al. 2014, Sundstrup, Jakobsen et al. 2014, Soe, Laosee et al. 2015, Kaliniene, Ustinaviciene et al. 2016) or incident shoulder pain (Gill, Shanahan et al. 2013). Incongruously, a study of a working population found an association of BMI with moderate but not with severe shoulder pain (Descatha, Dale et al. 2013). Moreover, the abovementioned systematic review did not observe any association between BMI and rotator cuff disorders (Viikari-Juntura, Shiri et al. 2008) nor did a case-control study find any link between BMI and rotator cuff tears requiring arthroscopy (Djerbi, Chammas et al. 2015). Moreover, there are several reports claiming that obesity did not elevate the occurrence of any upper extremity disorders (Descatha, Roquelaure et al. 2007), epicondylitis

(Walker-Bone, Palmer et al. 2012, Descatha, Dale et al. 2013, Herquelot, Bodin et al. 2013, Titchener, Fakis et al. 2013), de Quervain's disease (Petit Le Manac'h, Roquelaure et al. 2011), or wrist tendinopathy (Harris, Eisen et al. 2011).

Two theories have been proposed to elucidate the adiposity related mechanisms of tendinopathy (Abate, Schiavone et al. 2010); adiposity may impose a mechanical load on the load-bearing tendons, or it may affect tendons through systemic effects. Although obesity management may be an effective means of preventing serious diseases, such as non-insulin dependent diabetes mellitus, at present there are no studies suggesting that reducing body weight could protect individuals from UESTDs.

In conclusion, the results of the role of BMI in upper extremity pain and UESTDs are contradictory. Moreover, some crucial obesity related features such as the presence of low-grade inflammation have not been assessed in UESTD studies. More investigations are needed with large general population samples, especially those taking relevant confounders into consideration. For example, gender may modify the association between obesity and UESTDs. Stratified analyses should be carried out in order to clarify the sex-related differences in these putative associations.

2.3.3.2 Diabetes

Today, diabetes can be considered as a worldwide epidemic. The global prevalence of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5%, reflecting an increase in associated risk factors such as overweight or obesity (NCD-RisC 2016). Diabetes is known to be a risk factor for rotator cuff disorders, adhesive capsulitis, finger flexor tenosynovitis and Dupuytren's disease (Abate, Schiavone et al. 2013, Ranger, Wong et al. 2015). It is also a possible risk factor for carpal tunnel syndrome (Pourmemari and Shiri 2016). However, the role of diabetes in other UESTDs is less clear-cut.

Rotator-cuff tears are common in patients with diabetes (Abate, Schiavone et al. 2013). Moreover, a long duration of diabetes increases the risk of upper extremity pain, and tendinopathy in the finger flexor tendons and the rotator cuff (Raje, Cracknell et al. 2015, Ranger, Wong et al. 2015). One study investigating general population health data found that both oral antidiabetic drugs and insulin use were associated with rotator cuff disease (Titchener, White et al. 2014). Moreover, a case-control study carried out in a clinic specializing in managing diabetics observed a higher prevalence of shoulder tendinopathy among patients with type 2 diabetes compared to matched controls without diabetes, however, reporting only unadjusted prevalence

rates (Kidwai, Wahid et al. 2013). Elevated glucose levels in the pre-diabetic state may also be associated with a risk of rotator cuff disorders. Patients in an orthopaedic clinic undergoing surgery for rotator cuff tear had a significantly higher plasma glucose level within the normal glycaemic range compared to controls undergoing surgery for meniscal tear (Longo, Franceschi et al. 2009).

With regard to other UESTDs, a persistently elevated level of blood glucose has been associated with lateral epicondylitis in individuals over 40 years of age attending health check-ups (Otoshi, Takegami et al. 2015). Another cross-sectional study found an association between diabetes and epicondylitis, but only in the age and sex adjusted model (Shiri, Viikari-Juntura et al. 2006). Moreover, a cross-sectional study reported a higher prevalence of lateral and medial epicondylitis and De Quervain's disease among individuals with diabetes compared to those without diabetes, however reporting only unadjusted prevalence rates (Font, Castro-Santana et al. 2014). There are two cross-sectional studies and one case-control report that detected no association between diabetes and epicondylitis or de Quervain's disease (Petit Le Manac'h, Roquelaure et al. 2011, Walker-Bone, Palmer et al. 2012, Titchener, Fakis et al. 2013). Furthermore, two cohort studies could not find any evidence for an association between diabetes and wrist tendinitis (Harris, Eisen et al. 2011) or upper extremity tendon disorders (Descatha, Roquelaure et al. 2007) . However, the results of a meta-analysis showed that the prevalence of tendinopathy is increased among subjects with diabetes (Ranger, Wong et al. 2015). Moreover, in individuals with diabetes, biceps and rotator cuff tendon thickness may be increased without any signs of clinical tendinopathy (Akturk, Karaahmetoglu et al. 2002). The tendon thickening encountered in individuals with diabetes is largely a consequence of increased formation of advanced glycation end products (AGEs) in tendons, which triggers the activation of catabolic cytokines as well as the degeneration of the tendon matrix, leading to symptoms and functional impairment of the affected tendon structures (Mäkelä, Heliövaara et al. 1999, Abate, Schiavone et al. 2013).

In conclusion, rotator cuff disorders are a subgroup of UESTDs consistently related with diabetes. In addition, elevated glucose levels within the pre-diabetic range may have adverse effects on upper extremity tendons and may be related to UESTDs. However, it has to be stated that some studies investigating the role of diabetes in UESTDs have not been of high quality and furthermore, some of the associations appear to be somewhat inconsistent. Future studies examining the role of diabetes in UESTDs should recruit large general population samples and take into consideration all of the relevant confounders.

2.3.3.3 Dyslipidemia

The role of dyslipidemia in UESTDs is uncertain. The role of a high cholesterol level has been highlighted in patients with familial hypercholesterolemia, who often present with Achilles tendon xanthomas and are susceptible to pain in the Achilles tendon prior to the development of clinically defined xanthomas. Moreover, studies conducted in mice have suggested that in hypercholesterolemia, deposition of microscopic cholesterol particles inside tendons may cause tendon inflammation and subsequent degeneration (Beason, Abboud et al. 2011). The results of individual studies on the associations between lipids and upper extremity disorders have been inconsistent (Abboud and Kim 2010, Longo, Franceschi et al. 2010). However, a systematic review and meta-analysis revealed that the levels of total cholesterol, low-density lipoprotein cholesterol, high density lipoprotein cholesterol and triglycerides were associated with tendinopathy (Tilley, Cook et al. 2015). Nonetheless, it seems that the meta-analysis suffered from several limitations i.e. the reviewed studies were all cross-sectional or case control studies, with no prospective cohort studies being included. Furthermore, the included studies did not control for the putative associations of all known confounding factors and finally, publication bias was not assessed nor were the pooled estimates controlled for small-study effects.

2.3.3.4 Leisure time physical activity

To date, there are few certainties concerning the effects of leisure time physical activity and upper extremity strengthening exercises on upper extremity disorders. Some competitive sports activities may be responsible for injuries in the upper extremities (Hill, Collins et al. 2015). However, the role of leisure time physical activity in the primary prevention of non-specific and specific upper extremity disorders has not been thoroughly examined. It has been claimed that exercise may have a role in the secondary and tertiary prevention of upper extremity disorders (Desmeules, Boudreault et al. 2016). However, epidemiological studies examining the link between leisure time physical activity and upper extremity disorders have yielded inconsistent results.

Some studies suggest that regular physical activity may have beneficial effects on shoulder pain (van den Heuvel, Heinrich et al. 2005, Viikari-Juntura, Shiri et al. 2008, Mork, Holtermann et al. 2013) and upper extremity pain (Kim, Suh et al. 2015). On the other hand, there are other studies reporting either no association between physical activity and non-specific shoulder or upper extremity pain (Feng, Liang et al. 2014, Herin,

Vézina et al. 2014, Sundstrup, Jakobsen et al. 2014, Gremark Simonsen, Axmon et al. 2017), nor between physical activity and any specific upper extremity disorder (Werner, Franzblau et al. 2005, Shiri, Viikari-Juntura et al. 2006).

The number of studies published on physical activity and UESTDs is small and some of them recruited selected and small populations. Further prospective studies are therefore needed to elucidate the role of physical activity in UESTDs.

2.3.3.5 Smoking

Smoking is a known risk factor for a large number of health problems (Collaborators 2016). In 2015, throughout the world, 21.0% of men and 6.2% of women were current smokers (Collaborators 2016). In the same year, smoking was responsible for 148.6 million disability-adjusted life years globally and it was the second-leading risk factor for all disabilities in men and contributed to a large proportion of the global burden of diseases (Collaborators 2016). To date, however, virtually nothing is known about the role of smoking in upper extremity disorders.

There are some reports of an association of smoking with upper extremity pain (Gill, Shanahan et al. 2013, Mbutshu, Malonga et al. 2014, Sundstrup, Jakobsen et al. 2014), lateral epicondylitis (Shiri, Viikari-Juntura et al. 2006, Michienzi, Anderson et al. 2015), and shoulder impingement syndrome and rotator cuff tears (Bishop, Santiago-Torres et al. 2015, Djerbi, Chammas et al. 2015). On the other hand, a number of studies have not detected any association between smoking and upper extremity pain (Descatha, Teysseyre et al. 2012, Feng, Liang et al. 2014, Herin, Vézina et al. 2014, Pelissier, Fontana et al. 2014) or between smoking and upper extremity soft tissue disorders (Leclerc, Landre et al. 2001, Werner, Franzblau et al. 2005, Descatha, Roquelaure et al. 2007, Pullopdissakul, Ekpanyaskul et al. 2013, Fan, Silverstein et al. 2014).

The design of some of those studies which did detect a positive association between smoking and upper extremity disorders was cross-sectional. Furthermore, some of these studies did not control for all confounding factors. The association between smoking and an upper extremity disorder can be confounded by the presence of occupational factors. A systematic review found an association between smoking and shoulder pain or disorders only in certain occupational populations (Viikari-Juntura, Shiri et al. 2008). Nonetheless, it is likely that smoking impairs the healing process (Ng, Huang

et al. 2015) and this may predispose individuals to recurrent upper extremity disorders (Gill, Shanahan et al. 2013).

2.4 ADIPOKINES

Adipokines are a family of inflammatory mediators classified according to their production from adipose tissue and macrophages residing in fat (Abella, Scotece et al. 2014). In addition to the classical pro-inflammatory cytokines released from fat tissue such as interleukins 1 and 6 and tumor necrosis factor alpha, the adipokine family now contains several recently discovered proteins such as leptin, adiponectin, resistin and visfatin (Lago, Dieguez et al. 2007). These newly characterized adipokines are multifunctional proteins that are participants in the low-grade inflammation encountered in obese subjects and they have been linked to the pathogenesis of metabolic syndrome and obesity related diseases (Abella, Scotece et al. 2014). Moreover, adipokines can be divided according to their ability to induce mainly either pro-inflammatory or anti-inflammatory effects. Adipokines modulate a wide range of inflammatory and autoimmune processes, which means that they have been implicated in many serious illnesses, for instance rheumatic diseases. A role of adipokines has been postulated in degenerative joint diseases, specifically rheumatoid arthritis and osteoarthritis (Abella, Scotece et al. 2014). The role of the recently described adipokines in UESTDs is unknown.

2.4.1 LEPTIN

Leptin is a protein mainly produced by adipocytes. Its serum levels correlate with obesity and its expression is higher in women than men (Lago, Dieguez et al. 2007, Krysiak, Handzlik-Orlik et al. 2012). Leptin induces catabolic activity in the cartilage such that its expression is higher in osteoarthritic cartilage than in normal cartilage (Poonpet and Honsawek 2014). Leptin enhances inflammation by stimulating the expression of pro-inflammatory cytokines in pathological conditions such as rheumatoid arthritis and ulcerative colitis and also in insulin resistance (Lago, Dieguez et al. 2007). An association has been reported between leptin and pain in the lower back (Shiri, Solovieva et al. 2008) and pain related to arthrosis in the shoulder joint and hand (Massengale, Lu et al. 2012, Gandhi, Perruccio et al. 2013).

2.4.2 ADIPONECTIN

Adiponectin is a peptide that possesses both anti- and pro-inflammatory activities (Krysiak, Handzlik-Orlik et al. 2012). Decreased adiponectin levels have been related to pathological metabolic conditions, such as type 2 diabetes mellitus, dyslipidemia, insulin resistance, and the metabolic syndrome (Lago, Dieguez et al. 2007, Krysiak, Handzlik-Orlik et al. 2012). Pro-inflammatory cytokines inhibit the expression of adiponectin in adipocytes (Lago, Dieguez et al. 2007). Conversely, adiponectin inhibits the expression of the pro-inflammatory cytokines but induces that of the anti-inflammatory cytokines (Lago, Dieguez et al. 2007). Adiponectin may exert protective effects on joints through its anti-inflammatory and anabolic properties, but may also promote osteoarthritis by enhancing pro-inflammatory catabolic activities in the cartilage (Poonpet and Honsawek 2014). An association has been found between the synovial fluid adiponectin level and shoulder pain, suggesting that adiponectin may have a role in pain (Gandhi, Perruccio et al. 2013)

2.4.3 VISFATIN

Visfatin is primarily a pro-inflammatory cytokine, associated with obesity and insulin resistance (Lago, Dieguez et al. 2007). Its production is induced by pro-inflammatory cytokines but at higher concentrations, it can stimulate the expression of the anti-inflammatory cytokines (Tilg and Moschen 2008). Studies conducted in patients with inflammatory bowel disease and rheumatoid arthritis found evidence of increased expression of visfatin (Lago, Dieguez et al. 2007). Little is known about the role of visfatin in common musculoskeletal disorders. The level of visfatin in synovial fluid and in the circulation is increased in patients with osteoarthritis (Poonpet and Honsawek 2014).

2.4.4 RESISTIN

Resistin is a pro-inflammatory adipokine mainly produced by circulating mononuclear cells and endothelial cells as well as to a limited extent by adipocytes in humans (Lago, Dieguez et al. 2007). Resistin induces the activity of pro-inflammatory cytokines and has been implicated in certain human diseases such as atherosclerosis, systemic lupus erythematosus, asthma, chronic colitis, rheumatoid arthritis and osteoarthritis (Filková, Haluzík et al. 2009, Krysiak, Handzlik-Orlik et al. 2012). The serum levels of resistin have been associated with radiographic hand osteoarthritis (Choe,

Bae et al. 2012) and the levels of synovial fluid resistin are elevated in patients with knee osteoarthritis (Koskinen, Vuolteenaho et al. 2014). Moreover, in subjects with rheumatoid arthritis, the resistin levels in plasma and synovial fluid are increased (Krysiak, Handzlik-Orlik et al. 2012).

2.5 INFLAMMATORY MARKERS IN UESTDS

2.5.1 MECHANISMS OF TENDON INFLAMMATION

Inflammation is the term describing the local accumulation of fluid, plasma proteins and white blood cells; it may be initiated by physical injury or a local immune response, also known as an inflammatory response (Janeway, Travers et al. 2005). In the tendon, activation of an inflammatory response is considered to require both intrinsic and external factors interfering with tendon matrix homeostasis (Wang 2006). Mechanical loading, which may be long lasting and low-level, exceeding the tendon's capability to adjust to the elevated mechanical demands, is fundamental in inducing a tendon inflammatory response (Riley 2005, Wang 2006). Persistent tendon loading increases collagen and proteoglycan synthesis by tendon fibroblasts (tenocytes), reforming the tendon matrix. Eventually, there is the appearance of a disorganised fibril formation and rounded fibroblasts with occasional microscopic ruptures of tendon fibrils (Riley 2005, Wang 2006). Tenocytes respond to mechanical loading and matrix changes by releasing many inflammatory mediators, especially interleukin 1 (IL-1), that induce the release of cyclooxygenase 2 (COX2), triggering a primary inflammation associated with pain and oedema (Riley 2004, Wang 2006). Alternatively, cells of the innate immunity system may sense strain-associated stress signals such as adenosine triphosphate (ATP) through activation of specific purinergic receptors P2Y (G-protein coupled receptors) and P2X (ligand-gated cation channels), stimulating the caspase-1 activating NALP3 inflammasome to produce active IL-1β (Martinon 2008, Saïd-Sadier and Ojcius 2012). IL-1, IL-6 and IL-8 and tumour necrosis factor alpha (TNFα) are characteristic biomarkers of the innate primary inflammatory response expressed primarily not only by inflammatory cells but also by other cell types such as fibroblasts and endothelial cells (Fitzgerald, O'Neill et al. 2001, Janeway, Travers et al. 2005). The primary cytokines, i.e. IL-1 and the pro-inflammatory cytokines induced by IL-1, activate inflammatory cells, e.g. macrophages, neutrophils and monocytes which then migrate into the injury site, stimulating the release of more cytokines that set in motion the process of tendon matrix degradation, vascular growth and fibroplasia. Tendon matrix remodelling is the result of the activity of the inflammatory mediators and is a characteristic feature of tendinopathy (Riley 2005, Wang 2006). For

instance, studies of rotator cuff disorders have detected a range of cytokines, matrix proteases and growth factors which are thought to be involved in matrix transformation in tendinopathy (Dean, Franklin et al. 2012).

2.5.2 INTERLEUKIN 1 FAMILY

2.5.2.1 General concepts of the interleukin 1 family

The interleukin 1 (IL-1) family comprises pro-inflammatory cytokines such as IL-1 and IL-1β, IL-18 and IL-33, receptor antagonists such as IL-1Ra and cell associated or soluble receptors such as sIL-1RII and sST2 (Garlanda, Dinarello et al. 2013). IL-1α present within the cell and its secreted form, IL-1β, are distinct molecular forms of IL-1 but with similar biological properties (Fitzgerald, O'Neill et al. 2001). IL-1β is a powerful inflammatory mediator and a key cytokine in the immunological regulation of human disease; its functions are controlled by negative regulators like IL1-Ra and the soluble decoy receptor sIL-1RII. IL-1β induces formation of prostaglandin E2 (PGE2) by the enzyme COX2, mediating pain and edema (Lee, Kim et al. 2004, Dinarello 2009). Other significant pro-inflammatory properties of IL-1β are its ability to increase the expression of adhesion molecules and to induce chemokines and angiogenesis. Chronic IL-1 induced inflammation with subsequent tissue remodelling is one characteristic feature of the pathobiology of several musculoskeletal disorders such as rheumatoid arthritis, osteoarthritis and degenerative intervertebral disc disease (Le Maitre, Hoyland et al. 2007, Dinarello 2009). Excess body mass increases IL-1 production, indicating that obesity can be viewed as an inflammatory condition.

IL-18 is an important IL-1 family pro-inflammatory cytokine involved in inflammatory joint disease such as rheumatoid arthritis, for example by stimulating cartilage degeneration (Arend, Palmer et al. 2008). IL-18 is linked to obesity and insulin resistance (Osborn, Gram et al. 2008) but it also has important roles in other inflammatory diseases, e.g. in systemic lupus erythematosus, psoriasis, Crohn's disease and allergy.

IL-33 is a pro-inflammatory cytokine; it is the ligand for the receptor ST2 (suppression of tumorigenicity 2). Both IL-33 and ST2 are biomarkers of Th2 responses (Arend, Palmer et al. 2008, Dinarello 2009). IL-33 contributes to joint inflammation and synovial hyperplasia, and is also involved in cardiovascular disease and certain allergic disorders such as asthma (Dinarello 2009). Increased levels of soluble ST2 (sST2) have been found in the serum of patients with inflammatory conditions such as asthma and

systemic lupus erythematosus as well as in the synovial fluid of patients with rheumatoid arthritis (Arend, Palmer et al. 2008). The soluble form of ST2 acts as a decoy receptor of IL-33 with anti-inflammatory effects. In mice with collagen-induced arthritis, it was observed that an intra-articular injection of sST2 could attenuate the joint inflammation (Arend, Palmer et al. 2008).

2.5.2.2 IL-1 family and UESTDs

Rather few investigators have examined the role of IL-1 in UESTDs. When this has been done, they have generally reported increased expression of IL-1 in different experimental settings, however some reports have been inconsistent. A study using a rat model mimicking work-related UESTDs, showed that exposure of rat forelimbs to excessive repetition increased the expression of IL-1 in the tendon as well as in the circulation (Barbe, Barr et al. 2003, Barbe, Elliott et al. 2008, Fedorczyk, Barr et al. 2010). It was also found that the infiltrating macrophages detected in rat peripheral forelimb tissues could be one source of the circulating IL-1. Inconsistently, a study implementing static loading of rabbit tendon detected a decline in IL-1 expression in the tendon (Asundi and Rempel 2008). Moreover, an investigation of experimental epicondylitis in a rabbit model showed that cumulative repetitive loading did not increase the expression of IL-1 in the flexor digitorum tendon (Asundi, King et al. 2008).

In cultured human flexor digitorum tendon cells, physical loading was found to induce the expression of IL-1β (Tsuzaki, Bynum et al. 2003). Studies of subacromial bursa specimens retrieved from patients undergoing rotator-cuff surgery have shown consistently increased expression of several proteins from the IL-1 family, e.g. IL-1α, IL-1β and IL-1Ra (Gotoh, Hamada et al. 2001, Sakai, Fujita et al. 2001, Blaine, Kim et al. 2005, Voloshin, Gelinas et al. 2005). Increased expression of IL-18 has been observed in specimens of torn supraspinatus tendons as compared with intact subscapularis tendons (Millar, Wei et al. 2009). In addition, a study comparing samples of torn supraspinatus tendons with intact subscapularis tendons in the same shoulder, which was intended to provide a relevant way of comparing the expression of pro-inflammatory cytokines in chronic tendinopathy with those in pre-clinical tendinopathy, detected a higher expression of IL-21 receptor in the subscapularis tendon, which may be interpreted as evidence of increased IL-1 family cytokine activity in early tendinopathy (Campbell, Smith et al. 2014).

There are only a few reports of IL-1 family cytokines in outpatient UESTD populations. A study of patients with upper extremity disorders with symptom duration less than 12 weeks reported a correlation between serum

levels of IL-1 and symptom severity scores, however, in the regression analyses, the association lost its statistical significance (Carp, Barbe et al. 2007). A study of patients with rotator cuff disorder conducted by Savitskaya and colleagues reported a correlation between serum IL-1β and the grade of degeneration as assessed by ultrasound imaging, showing the highest concentrations in individuals having tendon ruptures (Savitskaya, Izaguirre et al. 2011).

2.5.3 INTERLEUKIN 6 (IL-6)

IL-6 is a multifunctional cytokine secreted by both lymphoid and non-lymphoid cells regulating B and T cell functions, hematopoiesis and acute phase reactions (Fitzgerald, O'Neill et al. 2001). Some non-lymphoid cells also express IL-6 for instance macrophages, chondrocytes, fibroblasts and endothelial cells as well as adipocytes. IL-6 is the key mediator of the synthesis of acute phase C- reactive protein (CRP). Together with IL-1 and TNFα, IL-6 is a major cytokine in the pathogenesis of rheumatoid arthritis (Choy 2012) and osteoarthritis, promoting the destruction in the cartilage and the subchondral bone layer (Wojdasiewicz, Poniatowski et al. 2014). Some investigators have proposed a pain modifying role for IL-6 in degenerative joint disease (Wojdasiewicz, Poniatowski et al. 2014) and fibromyalgia (Mendieta, De la Cruz-Aguilera et al. 2016). A study of recent onset upper extremity disorders detected a correlation between the serum IL-6 concentration and symptom severity (Carp, Barbe et al. 2007). Increased expression of IL-6 has been found in samples of subacromial bursas in rotator cuff disease and also in torn rotator cuff tendons (Blaine, Kim et al. 2005, Voloshin, Gelinas et al. 2005, Ko, Wang et al. 2008). Moreover, in patients that were operated for CTS, levels of serum and carpal flexor tendon tenosynovium IL-6 were increased when compared to control samples of cadavers or in patients undergoing other hand surgical procedures (Freeland, Tucci et al. 2002).

2.5.4 INTERLEUKIN 8 (IL-8)

IL-8 is a pro-inflammatory chemokine produced by macrophages, predominantly attracting and activating neutrophils at the site of inflammation but also regulating other types of white blood cells such as basophils and lymphocytes (Fitzgerald, O'Neill et al. 2001). IL-8 is a potent angiogenic factor and therefore a plausible promoter of neovascularization in tendon disorders. IL-8 is associated with pain in patients with fibromyalgia

(Mendieta, De la Cruz-Aguilera et al. 2016). In patients with rotator cuff tear, the IL-8 level of shoulder joint fluid was associated with resting pain (Okamura, Kobayashi et al. 2015) . Moreover, there was evidence of elevated IL-8 expression in bursa samples of patients with adhesive subacromial bursitis (Yoshida, Funasaki et al. 2003). Furthermore, in patients with rotator cuff disorder, the levels of serum IL-8 were associated with the grade of rotator cuff degeneration (Savitskaya, Izaguirre et al. 2011).

2.5.5 TUMOR NECROSIS FACTOR ALPHA (TNFα)

TNFα is a potent pro-inflammatory cytokine with diverse roles in inflammation and immune functions (Fitzgerald, O'Neill et al. 2001). TNFα levels are elevated in obesity and insulin resistance (Trayhurn, Bing et al. 2006) and this cytokine also plays an important role in rheumatoid arthritis (Choy 2012) and osteoarthritis (Wojdasiewicz, Poniatowski et al. 2014). In osteoarthritis, the inflammatory stimulation evoked by TNFα is a potential pathway leading to pain induction (Lee, Ellman et al. 2013). In the above-mentioned upper extremity overuse model, increased expression of TNFα was found in serum as well as in tendon specimens of rats exposed to high repetition movements (Barbe, Elliott et al. 2008, Gao, Fisher et al. 2013). Several studies of subacromial bursa specimens retrieved after rotator cuff disorder surgery have detected increased expression of TNFα (Dean, Franklin et al. 2012). An association has also been found between serum TNFα levels and the severity of recent onset upper extremity disorder symptoms (Carp, Barbe et al. 2007).

2.5.6 TRANSFORMING GROWTH FACTOR BETA (TGFβ)

TGFβ is essentially an anti-inflammatory protein (Gorelik and Flavell 2002); it is involved in tissue remodelling, wound repair and haematopoiesis (Fitzgerald, O'Neill et al. 2001). TGFβ inhibits cell growth and promotes tissue fibrotic transformation of tissues by inducing collagen synthesis and angiogenesis, features typically seen in tendon disorders (Kovacs and DiPietro 1994). The role of TGFβ has been very little studied in UESTDs. In a rodent upper extremity overuse model, serum and tendon TGFβ was increased along with epitendon thickening in those rats exposed to excessive repetition (Gao, Fisher et al. 2013). An increased expression of TGFβ was found in subacromial bursa specimens of subjects with rotator cuff tears (Dean, Franklin et al. 2012).

2.5.7 C-REACTIVE PROTEIN (CRP)

CRP is an acute phase protein produced by the liver and induced mainly by IL-6 (Black, Kushner et al. 2004). In human tenocytes, however, CRP gene expression may be impaired by the presence of IL-6 (Busch, Girke et al. 2013). CRP functions as an innate immunity complement activator promoting phagocytosis through opsonisation (Black, Kushner et al. 2004). CRP has both anti- and pro-inflammatory properties i.e. it can induce the secretion not only of anti-inflammatory mediators IL-1Ra and IL-10, but also that of the pro-inflammatory cytokines IL-1, IL-6, IL-8, IL-18 and TNFα (Black, Kushner et al. 2004). CRP expression is increased in obesity and this phenomenon has been implicated in the chronic systemic low-grade inflammation associated with that condition (Debnath, Agrawal et al. 2016). An elevated circulating level of CRP (using cut point of 3mg/l) has been associated with an increased risk of ischaemic heart disease (Verma and Yeh 2003) and atherosclerosis (Jialal, Devaraj et al. 2004). The serum level of CRP increases in chronic inflammatory diseases such as rheumatoid arthritis (Rhodes, Fürnrohr et al. 2011). Moreover, CRP has been linked with osteoarthritis (Saberi Hosnijeh, Siebuhr et al. 2015). A study of patients undergoing knee or hip replacement found an association of CRP with pre-operative pain severity but not with the degree of osteoarthritis (Sturmer, Brenner et al. 2004). In a cross-sectional study of a population of adolescents, no association was observed between CRP levels and musculoskeletal pain (Bout-Tabaku, Michalsky et al. 2015), however, in a population of patients with chronic kidney disease, an elevated CRP level correlated with the severity of chronic musculoskeletal pain (Caravaca, Gonzales et al. 2016). A prospective study in patients with acute sciatica reported an association between higher serum CRP level with acute pain but not with chronic low back pain (Stürmer, Raum et al. 2005). The role of CRP in UESTDs has received little attention so far. There is one report of patients with recent onset upper extremity disorders which detected an association between serum CRP levels and the severity of symptoms (Carp, Barbe et al. 2007).

2.6 SUMMARY OF EXISTING INFORMATION AND GAPS IN OUR KNOWLEDGE

UESTDs are common health problems; previous research indicates rather consistently that age and physical work load factors play a role in their aetiology. On the other hand, the effects of lifestyle factors, e.g. physical exercise and smoking, and metabolic factors on UESTDs are uncertain. The pathological mechanisms in the process of tendon inflammation are still partly unresolved. Moreover, very little is known about the role of adipokines and inflammatory factors in UESTDs. There is some evidence emerging from work conducted in upper limb overuse models in rats and rotator cuff samples obtained during surgery that there may be elevated pro-inflammatory activity in UESTDs. Serum samples of selected patient populations have shown correlations between increased expression of pro-inflammatory cytokines and symptom severity as well as with degree of shoulder tendon degeneration. Nevertheless, these findings should be viewed with some caution. The evidence supporting the role of inflammatory biomarkers in UESTDs either during their early stage or throughout their natural course is lacking (Gold, Hallman et al. 2015). In addition, there are no study reports of biomarkers that might represent potential mediators between metabolic risk factors and UESTDs. Finally, no specific biomarker analyses have yet been developed for screening or diagnostic purposes in UESTDs (Saxton 2000, Gold, Hallman et al. 2015). In conclusion, as the findings of the associations between metabolic and inflammatory factors and UESTDs are largely based on a limited number of studies and reveal partly inconsistent results, more research is needed. This thesis addresses these deficits by applying a clinical epidemiological approach, using a population-based survey and also a clinical sample.

3 AIMS OF THE STUDY

The overall aim of this study was to assess the associations of metabolic factors and inflammatory related parameters with UESTDs.

The specific aims of the study were as follows:

To estimate the prevalence of shoulder joint pain and chronic rotator cuff tendinitis (article I)

To assess the associations of metabolic factors, particularly obesity, metabolic syndrome and adipokines with shoulder joint pain, chronic rotator cuff tendinitis, and pain intensity in incipient upper extremity soft tissue disorders (articles I-II).

To identify circulating inflammatory biomarkers in incipient upper extremity soft tissue disorders (article III).

To determine the effects of serum adipokine levels on recovery from upper extremity soft tissue disorders and to explore whether obesity modifies these effects (article IV).

4 METHODS AND MATERIALS

4.1 STUDY POPULATION

4.1.1 HEALTH 2000 SURVEY

The Health 2000 Survey, a nationwide study conducted by the National Institute of Health and Welfare, comprised all men and women aged 30 years or over living in Finland between autumn 2000 and spring 2001. A representative sample of the Finnish population was drawn by stratifying the population into five university hospital regions clustered into 16 health care districts, totalling 80 health care districts throughout the whole country. The 15 largest health care districts were sampled with probability 1, and then the probability proportional to size (PPS) method was used to sample the remaining 65 health care districts. Persons aged 80 years or over were recruited by doubling the sampling fraction (Aromaa A. 2004).

The primary population of the Health 2000 Survey consisted of 8028 subjects, of them 6354 (80%) participated in the home interview and the health examination. In the current study, subjects with missing information about shoulder disorders (N = 24) and those with clinically diagnosed rheumatoid arthritis and a positive rheumatoid factor (N = 93) were excluded and thus finally 6237 (78%) subjects were included in the analysis.

4.1.2 UPPER EXTREMITY PROJECT

4.1.2.1 Patients

The patients' recruitment was carried out in the Finnish Institute of Occupational Health (FIOH) between spring 2006 and fall 2008. Three occupational health service units in Helsinki delivering primary health care referred eligible patients who had sought medical advice for incipient UESTDs for further examination to the Work Physiatry Clinic of FIOH. Altogether 224 subjects were examined, of them 61 were excluded due to disqualification or missing information on fasting serum samples (see below). Ultimately, 163 actively working subjects with symptom duration of less than one month and meeting diagnostic criteria based on physical examination were included.

We excluded subjects whose main problem was a spinal disorder, advanced osteoarthritis, autoimmune disease, fibromyalgia, malignancy, or who had history of recent injury, former surgery related to the current problem, or the

presence of a deformity. Aiming to eliminate chronic disorders, we excluded also subjects with work absence for two weeks or longer prior to the medical examination, those needing sick leave immediately after the examination and those with three or more pain episodes of the same disorder during the past year. Furthermore, we excluded six patients with carpal tunnel syndrome, leaving 163 patients for the analysis. In addition to baseline, information was gathered at 4 weeks, 8 weeks and 12 weeks follow-up.

4.1.2.2 Controls

A control group was recruited from the Finnish Institute of Occupational Health. The controls were healthy volunteers free from upper extremity symptoms (N = 42). The working environment of the controls was largely comparable with the patients. Moreover, patients and controls were matched at group level for both age and sex.

4.2 OUTCOMES

4.2.1 HEALTH 2000 SURVEY

Before starting the study, all project nurses and physicians were trained to carry out the clinical assessments. All study participants were examined with a structured protocol, where nurses interviewed each individual about musculoskeletal symptoms and physicians carried out a standardized physical examination. Joint symptoms were inquired with a general question "Have you had joint pain, ache or motion tenderness in one or more joints during the preceding 30 days?" After this, the individual was asked to point out the painful joint regions on a manikin. Pain during the preceding 30 days in either the right or left shoulder joint was defined as unilateral shoulder joint pain and pain in both shoulders as bilateral.

Chronic rotator cuff tendinitis was defined as a history of pain in the rotator cuff region lasting for at least 3 months, as well as pain during the preceding month, and pain in one or more active resisted movements (abduction, external rotation, internal rotation) and/or painful arc in shoulder abduction. The examining physician classified the diagnostic certainty into two levels; possible with the two last criteria and probable with only one of the two last criteria being met, however these categories were combined in the analysis.

4.2.2 UPPER EXTREMITY PROJECT

Upper extremity soft tissue disorders

UESTDs were determined by a standardized protocol comprising symptom questions and clinical examination manoeuvers by a physician. Subsequently, two specialists in physical medicine and rehabilitation confirmed the clinical diagnosis according to the predetermined criteria. Specific upper extremity disorders included disorders of the shoulder (rotator cuff tendinitis, impingement syndrome), elbow (lateral and medial epicondylitis) and wrist (De Quervain's disease, peritendinitis, tenosynovitis and nerve entrapments). Non-specific upper limb pain was defined as local pain in the shoulder, elbow, forearm or wrist in the absence of specific upper extremity soft tissue disorder, or only partially meeting the diagnostic criteria for a specific upper extremity disorder.

Intensity of upper extremity pain

Upper extremity pain during the preceding week was assessed with a visual analogue scale (0=no pain, 100= highest pain intensity possible). In the analyses, pain intensity was dichotomized at the highest tertile (cut-point 60).

Recovery from UESTDs

Recovery from UESTDs was assessed by phone interviews at 2, 8 and 12 weeks follow-up. The question had four alternative responses: "recovered fully", "recovered substantially", "remained unchanged", and "exacerbated". In the analysis, recovery was dichotomized into "recovered fully or substantially" and "remained unchanged or exacerbated".

4.3 INDEPENDENT VARIABLES

4.3.1 HEALTH 2000 SURVEY

Individual factors included age, sex, and years of education. Smoking status was classified as never, former, occasional and current smoking. Pack years were estimated by multiplying the number of smoking years by the number of cigarettes smoked per day / 20. Alcohol consumption was grouped into four levels; none, light, moderate and heavy according to cut-points of equal-sized distributions of serving portions or drinks. Leisure time physical

activity was assessed by a single question and classified into three groups: ≤1, 2–3, and ≥4 times per week.

Information on physical workload factors was gathered during the interview and included current exposure to the following factors: working with hands above the shoulder level for at least 1h/ day, manual handling of loads heavier than 5 kg at least 2 times/minute for a minimum of 2h/day, manual handling of loads heavier than 20 kg for at least 10 times/day, working with a vibrating tool for at least 2h/day, work demanding high handgrip forces for at least 1 h/day, and repetitive movements of the hands or wrists for at least 2h/day.

Height, weight, waist circumference, and hip circumference were measured (WHO 2000). BMI was classified into underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9) and obesity (BMI ≥30.0). Waist circumference was classified into three groups; normal (< 94.0 cm for men and <80.0 cm for women), overweight (94.0-101.9 cm for men and 80.0-87.9 cm for women), and abdominal obesity (≥102.0 cm for men ≥88.0 cm for women). Waist-to-hip ratio was also classified into three levels: <0.9, 0.9-1.0, >1.0 for men, and <0.8, 0.8-0.9 and >0.9 for women.

The diagnosis of diabetes mellitus was based on fasting blood glucose ≥7.0 mmol/l (126 mg/dL) (Alberti and Zimmet 1998), and/or a known previous diagnosis of diabetes mellitus, or intake of glucose lowering medication. Insulin resistance (HOMA-IR) was determined as *serum insulin x glucose/ 22.5*. We defined metabolic syndrome according to the criteria of the American Association of Clinical Endocrinologists (Einhorn, Reaven et al. 2003) when at least 3 of the following criteria were present: 1) central obesity (waist circumference > 102 cm for men and > 88 cm for women); 2) high fasting triglycerides (>150 mg/dL); 3) low HDL cholesterol (< 40 mg/dL for men and < 50 mg/dL for women); 4) high blood pressure (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg); and 5) impaired fasting glucose (≥110 mg/dL).

4.3.2 UPPER EXTREMITY PROJECT

Individual factors included age, sex, smoking (never, former, occasional or current), and intake of antihypertensive, glucose lowering, antidepressive and lipid lowering medication and painkillers. Frequency of alcohol consumption was inquired and grouped into two levels: <2 times per week, or ≥2 times per week. The number of sessions of physical exercise per week for at least 30 minutes causing sweating or shortness of breath was inquired

and used to classify frequency of physical exercise into none or occasional, 1-2 times/week, or ≥3 times per week.

Height, weight, waist circumference and hip circumference were measured by standard procedures (WHO 2000) and body fat composition by the bioimpedance technique. BMI was calculated and grouped into underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9) and obese (BMI ≥30.0). Patients' and controls' fasting blood samples were collected to measure serum levels of glucose, cholesterol, triglycerides and high sensitive C-reactive protein (CRP).

The patients were enquired by the examining physician about the frequency of heavy lifting, duration of working with hand above shoulder level, prolonged forceful gripping, as well as pinch grip that either required exertion or a deviated wrist posture, and the use of vibrating tools. Each factor was dichotomised using a cut-off point of being exposed for ≥10% of the work time during a workday.

We assessed job strain using the 14-item Job Content Questionnaire (Karasek, Brisson et al. 1998), and dichotomized job demands and job control at the median to create a job strain variable. Fear-avoidance beliefs were assessed using four items adapted from the study of Waddell and co-workers (Waddell, Newton et al. 1993). We used the score of 18 as the cut-off to define elevated fear-avoidance beliefs.

We applied the patient health questionnaire-9 (PHQ-9) to assess depressive symptoms (Kroenke, Spitzer et al. 2001), and used the cut-off value of ≥ 5 to define mild to severe depressive symptoms. Sleep disturbance was defined as often or always waking during the night or in the early hours. We defined the metabolic syndrome according to the revised National Cholesterol Education Program (NCEP) classification (Grundy, Brewer et al. 2004), fulfilling at least three of the following criteria: 1) central obesity (waist circumference ≥ 102 cm for men and ≥88 cm for women); 2) high fasting triglycerides (> 150 mg/dL or drug treatment for elevated triglycerides); 3) low HDL cholesterol (< 40 mg/dL for men and < 50 mg/dL for women, or drug treatment for reduced HDL); 4) high blood pressure (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or antihypertensive drug treatment with a history of hypertension); and 5) impaired fasting glucose (≥100 mg/dL or drug treatment for elevated glucose values).

We determined several serum inflammatory biomarkers interleukin 1 alpha and beta (IL-1α and IL-1β), interleukin 1 receptor antagonist (IL-1Ra), soluble interleukin 1 receptor 2 (sIL-1RII), interleukin 33 (IL-33), sST2, interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 18 (IL-18), and tumor

necrosis factor α (TNFα), and four adipokines - leptin, adiponectin, resistin and visfatin by Luminex® and enzyme linked immunosorbent assays.

4.4 STATISTICAL ANALYSES

4.4.1 HEALTH 2000 SURVEY

Population weighting was used for prevalence rates, odds ratios (OR), and their confidence intervals (CI) to correct for any disproportionate selection of population subsets and to adjust for age, sex, residential district, and language distributions in order to represent the Finnish general population. We conducted a multinomial logistic regression for shoulder joint pain (no, unilateral, bilateral) and a logistic regression for chronic rotator cuff tendinitis. The estimates were controlled for age, sex, education, working with hands above the shoulder level, manual handling of loads heavier than 5 kg or heavier than 20 kg, working with a vibrating tool, work demanding high handgrip forces, and repetitive movements of the hands or wrists. We also performed sex-specific analyses. Stata, version 10 software was used to conduct survey analyses.

4.4.2 UPPER EXTREMITY PROJECT

Cross-sectional design

We devised logistic regression models to study the associations of metabolic factors and adipokine levels with upper extremity pain intensity. We first performed six age- and sex-adjusted regression analyses to identify significant factors within each of the following families: 1) weight-related factors, 2) lipids, 3) other metabolic factors, 4) adipokines, 5) lifestyle factors other than overweight/obesity (smoking, alcohol consumption and physical exercise), and 6) work-related factors. The final regression model included all significant factors derived from the six age- and sex-adjusted models. We also performed a stratified analysis to assess whether the effects of adipokines differed between overweight and non-overweight subjects. We used SPSS, version 20.0 software to perform the analysis.

Case control design

We used chi-squared test for categorical variables and unpaired two-sample *t* test (Welch's test) for continuous variables to test for a statistically

significant (two-tailed P <0.05) difference between cases and controls. We conducted an unconditional logistic regression to investigate the associations between cytokine concentrations and UESTDs. The estimates were controlled for age, sex, smoking, body mass index, sleep disturbance, physical activity and alcohol consumption. Mean BMI differed between the cases and controls. We therefore used a stratified analysis to explore whether the observed associations between cytokines and UESTDs are due to BMI. Moreover, we corrected for multiple testing using the Bonferroni correction. We used Stata, version 8.2 software in the analysis.

Longitudinal design

We used generalized estimating equation (GEE) to study the effects of adipokine levels on recovery from UESTDs. The estimates were controlled for age, sex, follow-up time, physical activity, alcohol consumption, smoking, body mass index, sleep disturbance and job strain. We performed subgroup analyses for tendon disorders and for non-specific upper limb pain. Moreover, we explored whether the effects of the adipokines on the recovery from UESTDs were modified by overweight/obesity using a stratified analysis. We used Stata, version 10 software for the analysis.

4.5 ETHICAL STATEMENT

The Coordinating ethics committee of Helsinki University Hospital district approved this study on August 15th 2005. A supplementary ethical approval was given on April 3rd 2007 regarding the serum biomarker study as well as allowing for recruiting a control group.

5 RESULTS

5.1 HEALTH 2000 SURVEY (STUDY I)

The mean age of the study population was 52 years and the mean BMI was 26.2 kg/m^2 (Table 1). One fourth of the subjects were current smokers and a similar percentage exercised four times or more per week. Sixteen percent of the subjects reported shoulder joint pain and 2.8% had possible or probable chronic rotator cuff tendinitis.

Table 1 *Background characteristics of the study subjects who were free from rheumatoid arthritis (N=6,237), weighted proportion or mean, Health 2000 Survey, 2000-2001*

Characteristic	%	Mean
Mean age		51.9
Years of education		11.3
Body mass index (kg/m^2)		26.2
Waist circumference (cm)		92.9
Hip circumference (cm)		101.5
Insulin resistance		2.5
Current smoking	25.9	
Exercise (times/week)		
≤1	40.9	
2–3	32.6	
≥4	26.5	
Metabolic syndrome	30.5	
Diabetes		
Type 1	0.6	
Type 2	5.0	
High C-reactive protein (>3 mg/L)	16.7	
Shoulder joint pain		
Unilateral	9.5	
Bilateral	6.3	
Chronic rotator cuff tendinitis		
Possible	1.6	
Probable	1.2	

5.1.1 SHOULDER JOINT PAIN (STUDY I)

Body mass index, waist circumference and waist-to-hip ratio were associated with both unilateral and bilateral shoulder joint pain after adjustment for age, sex, education and physical workload factors (Table 2). Moreover, individuals with type 2 diabetes had an increased prevalence of shoulder joint pain. Smoking, leisure time physical activity, metabolic syndrome, insulin resistance and C-reactive protein were not associated with unilateral or bilateral shoulder joint pain.

In the sex-specific analyses, current smoking was associated with unilateral shoulder pain in men, with the strongest association detected in those men who had smoked more than 20 pack-years (OR = 1.9, 95% CI 1.3-2.9). Women who had smoked for 10-20 pack-years showed an increased prevalence of bilateral shoulder pain (OR = 1.8, 95% CI 1.0-3.1). With respect to weight related factors, abdominal obesity in terms of waist circumference or waist-hip ratio showed the strongest associations with unilateral shoulder pain in men (OR = 1.8, 95% CI 1.3-2.5 for waist circumference and 2.4, 95% CI 1.3-4.4 for waist-hip ratio) and bilateral shoulder pain in women (OR = 2.5, 95% CI 1.6-4.0 for waist circumference and 1.8, 95% CI 1.1-3.1 for waist-hip ratio). The metabolic syndrome (OR = 1.5, 95% CI 1.2-1.9) and type 2 diabetes (OR = 1.7, 95% CI 1.0-2.9) were associated with unilateral shoulder pain in men. High CRP values were associated with bilateral shoulder pain in women (OR = 1.4, 95% CI 1.0-2.1).

Table 2 *Odds ratios of unilateral or bilateral shoulder joint pain with respect to lifestyle and metabolic factors, Health 2000 Survey, 2000-2001*

Characteristic	Unilateral		Bilateral	
	OR*	95% CI	OR*	95% CI
Smoking status				
Never smoker	1		1	
Former smoker	1.02	0.82-1.26	0.98	0.74-1.29
Occasional smoker	1.01	0.64-1.60	0.56	0.27-1.19
Current smoker	1.09	0.86-1.39	0.84	0.60-1.17
Exercise (times/week)				
≤1	1		1	
2–3	1.22	0.99-1.50	0.86	0.66-1.13
≥4	0.80	0.63-	0.79	0.60-1.05
Body mass index				
Normal	1		1	
Underweight	0.34	0.07-1.54	0.34	0.04-2.69
Overweight	1.24	1.03-1.49	1.24	0.94-1.63
Obese	1.40	1.09-1.79	1.48	1.06-2.08
Waist circumference				
Normal	1		1	
Increased	1.65	1.31-2.08	1.35	0.99-1.82
Obese	1.62	1.30-2.03	1.66	1.25-2.20
Waist-to-hip ratio				
Normal	1		1	
Increased	1.17	0.91-1.52	1.37	0.90-
Obese	1.40	1.04-1.88	1.82	1.17-2.84
Metabolic syndrome	1.14	0.95-1.35	1.15	0.93-1.44
Insulin resistance, per each standard deviation	1.01	0.99-1.02	1.01	0.99-1.02
Diabetes				
Type 1	-		1.87	0.53-6.53
Type 2	1.48	1.08-2.04	1.55	0.99-2.43
C-reactive protein (high >3 mg/L vs. low <3 mg/L)	1.15	0.90-1.45	1.29	0.97-1.71

**Controlled for age, sex, education and physical load factors*

5.1.2 CHRONIC ROTATOR CUFF TENDINITIS (STUDY I)

With respect to weight-related factors, only waist circumference was associated with chronic rotator cuff tendinitis after adjustment for age, sex, education and physical workload factors (Table 3). Smoking, leisure time physical activity, metabolic syndrome, insulin resistance, diabetes and C-reactive protein were not associated with chronic rotator cuff tendinitis. In the sex-specific analysis, in our male subjects, increased waist circumference (OR = 3.8, 95% CI 1.1-3.5) and type 1 diabetes (OR = 4.7, 95% CI 1.1-20.3) were associated with chronic rotator cuff tendinitis.

Table 3 *Odds ratios of chronic rotator cuff tendinitis by lifestyle and metabolic factors, Health 2000 Survey, 2000-2001*

Characteristic	OR*	95% CI
Smoking status		
Never smoker	1	
Former smoker	1.14	0.78-1.67
Occasional smoker	0.43	0.15-1.24
Current smoker	0.85	0.50-1.41
Exercise (times/week)		
≤1	1	
2–3	1.31	0.91-1.89
≥4	1.09	0.74-1.62
Body mass index		
Normal	1	
Underweight	0.50	0.07-3.66
Overweight	1.28	0.88-1.85
Obese	1.48	0.93-2.37
Waist circumference		
Normal	1	
Increased	1.79	1.15-2.79
Obese	1.49	0.98-2.27
Waist-to-hip ratio		
Normal	1	
Increased	1.06	0.64-1.75
Obese	1.24	0.71-2.15
Metabolic syndrome	0.91	0.66-1.25
Insulin resistance, per each standard deviation increase	0.99	0.95-1.03
Diabetes		
Type 1	3.05	0.72-12.91
Type 2	1.12	0.63-2.02
C-reactive protein (high >3 mg/L vs. low <3 mg/L)	1.10	0.76-1.58

**Controlled for age, sex, education and physical load factors*

5.2 UPPER EXTREMITY PROJECT (STUDIES II, III AND IV)

The mean age of the patient population (N = 163) was 45 years, and 14% were men. Eleven percent were current smokers, 19% consumed alcohol twice or more often per week and 51% exercised 3 times or more per week. Fourteen percent were obese (BMI ≥ 30 kg/m²) and 25% were abdominally obese (waist circumference ≥102 cm in men and ≥88 cm in women).

Ten percent of the patients had high LDL cholesterol (>4.1 mmol/l), 4% low HDL cholesterol (<1.0 mmol/l) and 15% had high triglyceride levels (>1.7 mmol/l). Half (52%) of the patients reported having used painkillers for their upper extremity problem, most of them irregularly; 6% were receiving statin medication. The mean upper extremity pain intensity was 48 and the highest tertile cut-point of pain was 60 (study 2). Thirty six percent of the patients had a shoulder disorder, 31% epicondylitis, 13% experienced a wrist disorder and 20% had non-specific upper extremity pain. Overall, 27.5% reported full or substantial recovery after 8 weeks and 32% after 12 weeks of follow-up (study 4).

5.2.1 UPPER EXTREMITY PAIN (STUDY II)

In age- and sex-adjusted models, waist circumference, levels of HDL cholesterol and triglycerides, the concentration of the adipokine visfatin, alcohol consumption and job strain were associated with upper extremity pain. Waist circumference (OR = 2.9, 95% CI 1.1-7.3 for obesity), a low level of HDL cholesterol (OR = 3.9, 95% CI 1.4-10.1), a high level of triglycerides (OR = 2.6, 95% CI 1.0-6.8) and a high level of the adipokine, visfatin (OR = 1.4, 95% CI 1.0-2.1) were associated with upper extremity pain after adjustment for age, sex, alcohol consumption, job strain, depressive symptoms and regular statin medication use. The association between low HDL cholesterol and upper extremity pain did not change after further adjustment for waist circumference (OR 3.2, 95% CI 1.1-9.0). However, the association between high triglycerides and upper extremity pain did not remain statistically significant after further adjustment for waist circumference (OR = 2.3, 95% CI 0.8-6.8). Interestingly, the visfatin concentration was associated with upper extremity pain in both overweight and non-overweight subjects.

5.2.2 UPPER EXTREMITY SOFT TISSUE DISORDERS (STUDY III)

The patients had a higher mean BMI (25.5 ± 4.4 vs. 23.1 ± 2.9 kg/m^2, *P* <0.001), and a higher mean waist circumference (83.9 ± 12.7 vs. 80.0 ± 9.5 cm, *P* <0.044) than the controls. Moreover, sleep disturbance was more prevalent among the patients than controls (31% vs. 13%, P = 0.016). The groups did not differ with respect to smoking, alcohol consumption or leisure-time physical activity.

Serum levels of sIL-1RII and sST2 cytokines were significantly higher in the patients with UESTDs than in the controls after adjustment for age, sex, smoking, body mass index, physical activity, alcohol consumption, and sleep disturbance. Moreover, the serum level of IL-18 cytokine was significantly lower in the patients compared with the controls. The associations of sIL-1RII and sST2 with UESTDs were independent of BMI. Patients with low BMI (≤24.5 kg/m2) as well as those with high BMI (>24.5) had higher levels of sIL-1RII than the controls.

5.2.3 RECOVERY FROM UPPER EXTREMITY SOFT TISSUE DISORDERS (STUDY IV)

A high resistin level at baseline predicted a higher recovery rate from UESTDs during 8 weeks' follow-up (OR = 1.53, 95% CI 1.15-2.04 for 1-SD increase) after adjustment for age, sex and follow-up time. In a stratified analysis taking into account overweight or obesity, high resistin level (OR = 1.66, 95% CI 1.21-2.29 for 1-SD increase) and high visfatin level (OR = 1.91, 95% CI 1-18-3-10 for 1-SD increase) at baseline predicted a better recovery rate from UESTDs in normal weight subjects (BMI <25 kg/m^2) after controlling for age, sex and follow-up time. The associations between adipokine concentrations and recovery were non-significant in overweight or obese subjects. Moreover, high levels of resistin (OR = 1.52, 95% CI 1.08-2.11 for 1-SD increase) and visfatin (OR = 1.47, 95% CI 1.03-2.08 for 1-SD increase) at baseline predicted a better recovery rate from tendon disorders after controlling for age, sex, follow-up time and BMI. In contrast, the associations between adipokine levels and recovery from non-specific upper limb pain were non-significant.

6 DISCUSSION

6.1 MAIN FINDINGS

The findings of this study indicate that the prevalence of shoulder joint pain in the past month was 16% whereas that of possible or probable chronic rotator cuff tendinitis was 3% in a representative sample of the general population. In patients with incipient conditions, every third reported full or substantial recovery from UESTDs within three months.

We studied several metabolic factors but only obesity and type 2 diabetes were associated with the prevalence of shoulder joint pain. Moreover, obesity was associated with chronic rotator cuff tendinitis. Serum interleukin 1 family receptor sIL-1RII and sST2 and the pro-inflammatory cytokine, IL-18, levels were associated with UESTDs in the study among patients with incipient disorders and their age and sex matched controls. In patients with incipient UESTDs, lower levels of HDL cholesterol, and higher levels of triglycerides and adipokines were associated with greater intensity of upper limb pain. Moreover, adipokine levels predicted recovery from UESTDs.

6.2 PREVALENCE AND RECOVERY RATE

The prevalence estimate for shoulder pain found in this study falls within the range of 12% to 30% in the past month which has been reported in previous studies (Luime, Koes et al. 2004, Miranda, Viikari-Juntura et al. 2005, Cole, Gill et al. 2009). The prevalence of rotator cuff tendinitis was about half of that previously reported (Walker-Bone, Palmer et al. 2004, Roquelaure, Ha et al. 2009). One reason for this discrepancy may be that we included only those cases with symptoms lasting more than three months.

Our recovery rate of UESTDs is comparable to the values reported in other populations. In a clinical trial of exercise programs among patients with supraspinatus tendinopathy, 15% of cases reported recovery after one month of follow-up and 40% after three months (Şenbursa, Baltaci et al. 2011). A systematic review has found that half of new incident shoulder disorder episodes recover within 6 months (Kuijpers, van der Windt et al. 2004). A study investigating the prognosis of shoulder tendinopathy in employees doing repetitive work estimated that after 10 months about every second individual had no longer symptoms (Bonde, Mikkelsen et al. 2003). A study into lateral epicondylitis found that 37% reported no or minimal elbow pain after 2 months of physiotherapy and 38% reported no elbow pain after 6 months of successive physical therapy or alternative treatments such as

massage or pain killers (Waugh, Jaglal et al. 2004). In general practice, about every third (34%) of incident elbow complaints have shown full or substantial recovery after three months (Bot, van der Waal et al. 2005).

Overall, the findings of the current and previous studies indicate that UESTDs are relatively persistent conditions. Moreover, repeated exposure to physical load factors and an adverse metabolic environment may affect the healing process.

6.3 OVERWEIGHT AND OBESITY

With respect to the investigated metabolic factors, both general and abdominal obesity were associated with shoulder joint pain and chronic rotator cuff tendinitis. According to one review, obesity is associated with tendon disorders in the shoulder, elbow and wrist (Gaida, Ashe et al. 2009). However, the case studies included in that review controlled for a limited number of confounders, which may have resulted in some overestimation of the actual associations. Many longitudinal studies have not found any association between BMI and shoulder pain (Lamy, Descatha et al. 2014, Kooijman, Barten et al. 2015). Obesity may, however, increase the risk of shoulder pain in individuals with hypermobile joints (Tobias, Deere et al. 2013). With only one possible exception, previous studies on rotator cuff disorders or other UESTDs have not included assessments of abdominal obesity (Shiri, Viikari-Juntura et al. 2006).

There is no consensus on the pathways connecting obesity to UESTDs but two hypotheses have been presented to explain the possible mechanisms of upper extremity tendinopathy, one suggesting tendon damage caused by higher physical loads due to increased arm mass and the other implicating processes linked with the systemic inflammation triggered by adiposity (Abate, Schiavone et al. 2013, Franceschi, Papalia et al. 2014). Obesity increases the expression of several circulating biomarkers such as CRP and cytokines, e.g. IL-1 and TNFα that have been associated with shoulder pain and soft-tissue disorders of the shoulder. The obesity-induced increase in the levels of circulating pro-inflammatory cytokines may increase pain sensitivity and maintain inflammation in the rotator cuff.

A large waist circumference is an indicator of visceral fat mass, which is a metabolic risk factor known to increase susceptibility to diabetes and atherosclerosis. Visceral fat is the major trigger of systemic pro-inflammatory biomarker expression and low-grade inflammation. Therefore, abdominal obesity as such may be a better metabolic risk marker than BMI

in future studies investigating the links between metabolic factors and UESTDs.

6.4 DIABETES

In the current study, type 2 diabetes was related to shoulder pain, but not rotator cuff tendinitis. Moreover, we found a non-significant association between type 1 diabetes and chronic rotator cuff tendinitis. There is one meta-analysis which found evidence of an increased risk of tendinopathy among subjects with diabetes (Ranger, Wong et al. 2015). Furthermore, diabetes has been shown to be associated with chronic rotator cuff tendinitis, rotator cuff tendon tears, frozen shoulder, finger flexor tenosynovitis (Viikari-Juntura, Shiri et al. 2008, Abate, Schiavone et al. 2013) and a variety of other musculoskeletal complaints (Molsted, Tribler et al. 2012).

In agreement with our findings, some studies have reported an association of diabetes with shoulder pain and disorders (Mäkelä, Heliövaara et al. 1999, Roquelaure, Ha et al. 2009, Molsted, Tribler et al. 2012, Titchener, White et al. 2014, Lin, Lin et al. 2015). However, the associations of diabetes with distal tendon disorders have not been investigated in studies with large populations. Diabetes was not associated with wrist tendinopathy in a prospective study among a working population (Harris, Eisen et al. 2011).

In patients with diabetes, advanced glycation end products (AGEs) are precipitated in the tendons of the rotator cuff. AGE accumulation causes tendon thickening and activates catabolic cytokines leading to tendon matrix degeneration, a possible factor predisposing to shoulder pain in individuals with type 2 diabetes (Abate, Schiavone et al. 2013).

6.5 DYSLIPIDEMIA

In patients with incipient UESTDs, HDL cholesterol and triglyceride levels were associated with upper limb pain intensity. This relationship between lipids and upper limb pain is a novel finding although there are two previous studies that reported an association between HDL cholesterol and spinal pain (Schell, Theorell et al. 2008, Heuch, Heuch et al. 2010).

The role of lipids in UESTDs is unclear. Tendon health may be affected by the cholesterol level (Tilley, Cook et al. 2015). Cross-sectional studies on the association between serum lipids and rotator cuff tendon tears have shown inconsistent results (Scott, Zwerver et al. 2014). Moreover, a population-based cross-sectional study did not find an association between serum lipids

and epicondylitis (Shiri, Viikari-Juntura et al. 2006). In contrast, two cohort studies reported an association between dyslipidemia and rotator cuff disorders (Djerbi, Chammas et al. 2015, Lin, Lin et al. 2015).

HDL cholesterol is an antiatherogenic particle attenuating inflammation and as such may be associated with pain (Lowenstein and Cameron 2010). Moreover, triglycerides may serve as a systemic innate immunity stress signal that activates pain perception (Hotamisligil 2006, Martinon 2008).

6.6 INFLAMMATORY BIOMARKERS

In the current study, serum interleukin 1 family receptor sIL-1RII and sST2 and pro-inflammatory cytokine IL-18 levels were associated with UESTDs. These findings may point towards IL-1 and IL-33 mediated inflammatory processes and down-regulation of IL-18 during the early stage of UESTDs. Serum levels of sIL-1RII and sST2 and IL-18 correlated positively with BMI in both patients and controls. Moreover, the associations between sIL-1RII and sST2 and IL-18 with UESTDs remained significant even after adjusting for BMI and other potential confounders as well as in stratified analysis by BMI, suggesting that these factors have independent roles in UESTDs.

We found increased levels of CRP in women with bilateral shoulder pain, suggesting that high circulating concentrations of this protein may be associated with higher susceptibility to bilateral shoulder pain. A systemic condition or a local process in the shoulders increasing circulating CRP could be possible mechanisms triggering bilateral shoulder pain. However, the CRP molecule per se may induce pro-inflammatory activity and therefore might be a potential independent factor modifying inflammatory processes in the shoulder (Verma, Li et al. 2002).

As far as we are aware, there are three studies in outpatient populations which have previously reported an association between serum biomarkers and upper extremity disorders (Carp, Barbe et al. 2007, Savitskaya, Izaguirre et al. 2011, Matute Wilander, Kåredal et al. 2014). However, these studies suffered from some methodological limitations that must be considered when assessing their conclusions. The study of Carp and colleagues, showing associations of CRP and TNFα with upper extremity disorder severity, was carried out in a small population of 22 patients and only nine controls. Moreover, after excluding patients with sprain or carpal tunnel syndrome from the analysis, only 12 cases of UESTDs were left in the analysis. The study of Savitskaya and colleagues, which detected a link between IL-1 and

IL-8 and degenerative rotator cuff tendinopathy, reported only the correlations between the serum biomarker levels and rotator cuff ultrasound findings. Furthermore, that study did not control the associations for known confounders such as age, sex and BMI. In the third study (Matute Wilander, Kåredal et al. 2014), increased levels of serum inflammatory markers were associated with pain in the neck and shoulder among 35 female cashiers but it did not report associations of the biomarkers with shoulder pain exclusively.

Previous studies in humans have suggested that there is elevated expression of IL-1 in the late stage of rotator cuff disorders (Gotoh, Hamada et al. 2001, Sakai, Fujita et al. 2001, Blaine, Kim et al. 2005, Voloshin, Gelinas et al. 2005) but the current study's finding of these biomarkers in the early stage of UESTDs is novel. Therefore, increased soluble receptor IL1RII and ST2 transcription may occur in the early phase of UESTDs in an attempt to combat the actions of IL-1 and IL-33. The finding of a decline in IL-18 levels, suggesting reduction of IL-18 transcription triggered in incipient UESTDs is also new and is opposite to the reports in patients with rheumatoid arthritis and osteoarthritis, who exhibit an increased expression of IL-18 (Shao, Feng et al. 2009). In addition, the activity of the IL-1 family cytokines may indicate the presence of innate immunity patterns in incipient UESTDs (Garlanda, Dinarello et al. 2013).

6.7 ADIPOKINES

We found an association between the level of visfatin and upper limb pain in our cross-sectional study. In the longitudinal study, baseline levels of two adipokines, resistin and visfatin, predicted recovery from UESTDs up to 8 weeks. First, the findings indicate that adipokines may modify upper extremity soft-tissue pain in incipient disorders. Second, adipokines may exert anti-inflammatory effects on UESTDs during the acute or subacute stage, generally considered to last from 6 to 12 weeks from the onset of symptoms, and we speculate that these adipokines may influence the recovery from UESTDs.

To date, no previous study has found evidence of a role for adipokines in UESTDs. Adipokines have been recognized in musculoskeletal disorders as mediators of joint inflammation (Lago, Dieguez et al. 2007); for example, both resistin and visfatin have been reported to participate in the pathogenesis of osteoarthritis and rheumatoid arthritis by modifying disease activity (Toussirot, Streit et al. 2007, Rho, Solus et al. 2009, Choe, Bae et al. 2012, Duan, Hao et al. 2012). Visfatin promotes the pro-inflammatory

cytokine activity of IL-1 and IL-6, which are known mediators of joint inflammation (Lago, Dieguez et al. 2007).

In the current study, both resistin and visfatin were associated with recovery from UESTDs. Both adipokines are known to function bidirectionally i.e. in addition to their pro-inflammatory role, they evoke anti-inflammatory responses such as an increase in the level of TGFβ (Song, Lee et al. 2008, Son, Ahn et al. 2010, Kang, Kim et al. 2011), which has also been recognized in UESTDs (Bedi, Maak et al. 2012). TGFβ participates in healing and fibrogenic remodeling of tendon (Wang 2006). TGFβ may, therefore, be a potential cytokine that promotes recovery from UESTDs. Additionally, resistin has been found to participate in calcification processes (Burnett, Lee et al. 2005), and this could represent a link with the calcium deposits found in rotator-cuff tendinopathy.

6.8 STUDY STRENGTHS

Health 2000 Survey

The study population of *the Health 2000 survey* was representative and relatively large, which increased the reliability of the estimates of shoulder pain and rotator cuff tendinitis. In this respect, the findings can be generalized to the adult Finnish population. The examining nurses and physicians underwent a training course to ensure uniformity of the study protocol, which included structured interviews and clinical examinations of the participants. We investigated a wide set of metabolic risk factors such as several indicators of obesity and dyslipidemia.

Upper extremity project

Recruiting patients with incipient disorders allowed us to assess the early pathological processes involved in UESTDs. Moreover, this study was longitudinal and the response rates to the follow-up phone interviews were high. Case definition of UESTDs was based on explicit diagnostic criteria and the final diagnosis was agreed between three specialists in physical and rehabilitation medicine and occupational health. We measured several types of cytokines and adipokines which are believed to display associations with musculoskeletal disorders.

6.9 STUDY LIMITATIONS

Health 2000 Survey

A limitation of the Health 2000 Survey was cross-sectional design and therefore it does not allow causal inference. The chronological relationship between the exposures and shoulder pain or rotator cuff tendinopathy cannot be explored in studies with a cross-sectional design. Many of the studied lifestyle factors are long lasting in their nature. Although shoulder disorders may be also chronic in their nature, it seems reasonable to postulate that the studied lifestyle factors preceded rather than being a consequence of the onset of shoulder problems.

We did not assess sleeping posture habits. Unilateral shoulder pain can be provoked or exacerbated by lying on the painful side during sleep (Kempf and Kongsted 2012). Therefore, lack of controlling for sleeping posture exposure may have caused an overestimation of the role of metabolic factors in unilateral shoulder pain.

Upper extremity project

A limitation of this study was the small sample size and its female preponderance, which limited statistical power and generalizability. Furthermore, the control group was a selected sample. A larger random sample of the general population, at least of the same size as the patient population, would have been preferable. The control group was not matched by age and sex at the individual level. The control group was more likely to have higher income, higher educational background, lower BMI and smaller waist circumference and suffer from less sleep disturbances than the patient group. These differences may have resulted in an overestimation of the associations between the biomarkers and UESTDs.

We used different criteria to define the metabolic syndrome in the upper extremity project and the Health 2000 Survey, which may reduce the comparability of the findings with respect to the obtained associations. Moreover, we did not measure cytokines and adipokines in the follow-up assessment and were therefore not able to study the associations of changes in the levels of the cytokines with recovery from UESTDs.

We used self-reported outcomes for pain and recovery. Perceived musculoskeletal pain varies between individuals and is affected by psychosocial factors, and this self-reporting can possibly lead to some inconsistencies (Linton 2000). In this study, several individual factors (job strain, fear avoidance beliefs, depression) may have caused inconsistent self-

reports of upper limb complaints, for which it was not possible to fully control.

Exposures to different work related factors were also based on individual self-reports that may have been modified by symptoms. For example, individuals living with pain may overestimate their physical load exposures (Viikari-Juntura, Rauas et al. 1996).

6.10 CONCLUSIONS

At present, little is known about the role of inflammatory and metabolic factors in upper extremity musculoskeletal disorders. A notable proportion of studies on the role of inflammatory biomarkers in UESTDs have been based on rotator cuff tissue samples or in animal models of limb overuse. Only a few studies have explored the role of metabolic factors in upper extremity musculoskeletal disorders other than shoulder disorders. In the past years, however, the number of studies on the role of serum biomarkers in UESTDs has increased.

This study included several different types of metabolic factors and serum biomarkers; it revealed novel associations between them and shoulder pain and UESTDs. With respect to the metabolic factors, obesity and diabetes were associated with shoulder pain and rotator cuff tendinopathy. In addition, obesity and serum lipid levels were associated with pain in incipient UESTDs. With respect the studied biomarkers of inflammation, CRP was associated with shoulder pain, IL-1 family proteins were associated with incipient UESTDs and adipokines were associated with pain arising from UESTDs and with recovery from UESTDs.

The study findings suggest that metabolic risk factors such as obesity and diabetes may create an environment that can be harmful to upper extremity structures. Moreover, the findings suggest that serum inflammatory biomarker levels may be associated with shoulder pain and incipient UESTDs. Consequently, two mechanisms of altered serum inflammatory biomarkers levels in UESTDs may be proposed. First, serum biomarker levels may be modified in association with a condition that has secondary effects causing damage to the upper extremity tissues. Second, serum biomarker alterations may be a sequela of a local pathological process in the soft-tissues of the upper extremities.

Furthermore, the study findings suggest that adipokines may be involved in UESTDs in both their early (i.e. acute) and advanced (i.e. subacute) stages by modifying pain or recovery.

However, the fundamental mechanisms linking the metabolic and inflammatory factors with the UESTDs remain unknown. Nonetheless, our results imply that studies on serum biomarkers might be useful for assessing inflammatory factors in UESTDs, being complementary to tissue sample studies.

The relationships of metabolic and inflammatory factors with UESTDs need further investigation. Future longitudinal studies should recruit larger samples, preferably a representative sample of the general population. Moreover, future studies should investigate diverse and new metabolic factors and biomarkers that also could function as mediators in the link between metabolic factors and UESTDs.

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