Associations of metabolic factors and adipokines with pain in incipient upper extremity soft tissue disorders: A cross-sectional study

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The associations of metabolic factors and adipokines with pain in incipient upper extremity soft tissue disorders: a cross-sectional study

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ABSTRACT

Objectives: Earlier studies have suggested associations between metabolic factors and musculoskeletal pain or disorders. We studied the associations of obesity, lipids, other features of the metabolic syndrome and adipokines (adiponectin, leptin, resistin, visfatin) with upper extremity pain in a clinical population with incipient UESTDs.

Design: A cross-sectional study.

Setting: Primary health care (occupational health service) with further examinations at a research institute.

Participants: Patients (N=163) seeking medical advice in the occupational health service due to incipient upper extremity symptoms with symptom duration of less than one month were referred for consultation to the Finnish Institute of Occupational Health from spring 2006 to fall 2008. We included all actively working subjects meeting diagnostic criteria based on physical examination. We excluded subjects meeting predetermined conditions.

Outcome measure: Pain intensity was assessed with visual analogue scale and dichotomized at the highest tertile (cut-point 60).

Results: Obesity (adjusted odds ratio (OR) for high waist circumference 2.9, 95% CI 1.1-7.3), HDL cholesterol (OR 3.9, 95% CI 1.4-10.1 for low level) and triglycerides (OR 2.6, 95% CI 1.0-6.8 for high level) were associated with pain intensity. Of four adipokines studied, only visfatin was associated with upper extremity pain (adjusted OR 1.4, 95% CI 1.0-2.1 for one standard deviation increase in level).

Conclusions: Abdominal obesity and lipids may have an impact on pain intensity in UESTDs. They may intensify pain through proinflammatory pain-modifying molecular pathways or by causing soft tissue pathology and dysfunction of their supplying arteries. Of four adipokines studied only one (visfatin) was associated with pain intensity. In the future, further studies are required to better understand the relationship between metabolic factors and UESTDs.

ARTICLE SUMMARY

Article focus:

- We studied the associations of metabolic factors, serum C-reactive protein and adipokines with upper extremity pain intensity among subjects with incipient upper extremity soft tissue disorders (UESTDs).

Key messages:

- Subjects with abdominal obesity, low levels of high-density lipoprotein (HDL) cholesterol, or high levels of the adipokine visfatin reported higher upper extremity pain intensity than those with normal waist circumference, higher levels of HDL cholesterol, or low levels of visfatin.
- Further studies are needed to understand the role of metabolic factors in UESTDs.

Strengths and limitations of the study:

- Strengths of the study include: 1) Metabolic factors and adipokines were measured, and 2) Patients with early stage of upper extremity soft tissue disorders were included in the study.
- Limitations of the study include: 1) Small sample size, 2) Cross sectional design of the study.

INTRODUCTION

Upper extremity pain is a common health problem in general populations. The prevalence of forearm pain during the preceding 30 days has been estimated at 8%, [1] and that of shoulder pain has ranged between 12% and 30%.[1-4] In the general population, one of five persons reports chronic upper extremity pain.[5] Common causes for upper extremity pain include soft tissue disorders, such as rotator cuff tendinitis, epicondylitis and tenosynovitis.[6]

Some studies have suggested an association between musculoskeletal pain or disorders and metabolic factors, such as obesity, lipids and hyperglycaemia.[7-9] In a French working population study, obese men and diabetic women had a significantly higher occurrence of upper extremity soft tissue disorders (UESTDs) compared to subjects without such metabolic disorders.[10] In addition, an association has been reported between carpal tunnel syndrome and serum lipids.[11 12]

Obesity is often an underlying factor for dyslipidemia and disturbances of glucose metabolism. It may cause a systemic low grade inflammation and increased pro-inflammatory activity with elevated cytokine levels.[13] Dyslipidemia may cause accumulation of lipids on musculoskeletal structures, e.g., tendons.[14 15] Advanced glycation end-products may accumulate in hyperglycaemia resulting in latent collagen and microvascular alterations.[16 17]

Adipokines are proteins largely released by adipocytes, typically showing increased production in obesity. Characteristically, they exert widespread effects on immunological processes for example by stimulating cytokine expression. Adipokines function also in musculoskeletal disorders, best documented in degenerative inflammatory joint

conditions.[18] We are not aware of studies on the role of adipokines in non-inflammatory upper extremity disorders.

We studied the associations of obesity, lipids, other features of the metabolic syndrome and adipokines with upper extremity pain in a clinical population with incipient UESTDs. We hypothesised that UESTD patients with obesity, dyslipidemia, high C-reactive protein and adipokines report higher levels of pain intensity than patients without these risk factors. Furthermore, we explored whether the associations of adipokines with upper extremity pain differ in overweight and non-overweight subjects.

METHODS

Patients

This cross-sectional study was a part of a larger project on metabolic and inflammatory factors in UESTDs. Included conditions were shoulder disorders, e.g., rotator cuff tendinitis, elbow disorders, e.g., humeral epicondylitis, and wrist disorders, e.g., tenosynovitis. Patients seeking medical advice in the occupational health service due to incipient upper extremity symptoms with symptom duration of less than one month were referred for consultation to the Finnish Institute of Occupational Health from spring 2006 to fall 2008. We included all actively working subjects meeting diagnostic criteria based on physical examination.[19]

We excluded patients whose main problem was a spine or cervical disorder, advanced osteoarthritis, autoimmune disease, fibromyalgia, malignancy, history of recent injury, former surgery related to the current problem, and presence of deformity. We also excluded 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.

Ethics Statement

The Coordinating Ethical Committee of Helsinki University Hospital District has approved this study on 16th of August 2006. All subjects signed an informed consent form before entering the study.

Outcome

Symptoms were determined by the examining physician. A standardized protocol was used that included symptom questions and clinical tests. Visual analogue scale was used to assess pain intensity during the preceding week (0=no pain, 100= highest pain intensity possible). Pain intensity was dichotomized at the highest tertile (cut-point 60).

Independent Variables

We measured body height and weight, and systolic and diastolic blood pressure with standard procedures. Waist circumference was measured halfway between the lowest rib and iliac crest, and hip circumference was measured at the trochanter level. We calculated body mass index (BMI) as body weight in kilograms / (height in meters)^2. The subjects were categorized according to BMI into underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9) and obese (BMI $\geq$30.0).[20] Waist circumference was grouped into three levels; in men < 94.0 cm, 94.0-101.9 cm, $\geq$102.0 cm and in women <80.0 cm, 80.0-87.9 cm and $\geq$88.0 cm.[20] Waist-to-hip ratio was calculated as a ratio of waist circumference and hip circumference and classified into three groups: in men <0.9, 0.9-1.0, >1.0 and in women <0.8, 0.8-0.9 and >0.9.[20 21] Body fat was measured by the whole body bioimpedance technique (InBody 720, South-Chorea). We calculated body fat index as total body fat mass in kilograms / (height in meters)^2. In addition, we inquired the use of regular drug treatment.

Fasting blood samples were analysed with Advia 1800® (Siemens Healthcare Diagnostics, USA) for serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density

lipoprotein (LDL) cholesterol, triglycerides and blood glucose as well as serum C-reactive protein (CRP). For lipids we applied clinical cut points recommended by the National Cholesterol Education Program (NCEP) of the National Institutes of Health.[22] We stratified lipid variables in tertiles in case the NCEP cut-points resulted in too small subgroups. Fasting glucose was stratified in tertiles. To identify the metabolic syndrome we used the revised NCEP classification,[23] requiring at least 3 of the following findings: 1) central obesity, defined as waist circumference ≥ 102 cm in men and ≥88 cm in women; 2) high fasting triglycerides, defined as ≥ 1.7 mmol/l (> 150 mg/dL) or drug treatment for elevated triglycerides; 3) low HDL cholesterol defined as < 1.0 mmol/l in men (< 40 mg/dL) and < 1.3 mmol/l (< 50 mg/dL) in women or drug treatment for reduced HDL; 4) elevated blood pressure, defined as 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, defined as fasting glucose ≥ 5.6 mmol/l (100 mg/dL) or drug treatment for elevated glucose.

High CRP was defined as ≥ 3.0 mg/l.[24] Serum leptin, adiponectin, resistin (DuoSet ELISA R&D systems) and visfatin (Human Visfatin ELISA Kit, AdipoGen) were determined with enzyme-linked immunosorbent assay kits according to the manufacturer's instructions. Adipokines were used as continuous variables and their associations were modeled for one standard deviation increase in their level.

Smoking was classified as never, former, occasional or current. Alcohol consumption was determined as frequency of drinking alcohol per time unit, categorized into none or ≤1 times per month, 2-4 times per month, or ≥2 times per week. Physical exercise was defined as the number of sessions per week of physical activities for at least 30 minutes

causing sweating or shortness of breath and categorized into none or sometimes, 1-2, 3-4, or ≥5 times per week.

Exposure to physical load factors was assessed with an interview by a physician. The patients were inquired 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 deviated wrist posture, and the use of vibrating tools. Each factor was dichotomized using a cut-off point of being exposed for ≥10% of the work time during a workday.

We assessed fear-avoidance beliefs with the 4-item Physical Activity subscale of the Fear-Avoidance Beliefs Questionnaire:[25] "physical activity makes my symptoms worse"; "if my symptoms become worse, it means that I should stop what I was doing"; "my pain is caused by work"; and "I should not continue in my present job because of the symptoms". Each item had a 7-point scale from "totally disagree" to "totally agree". We defined fear-avoidance beliefs as high when the score was ≥18 (of maximum of 24).

We evaluated job strain using the "14 item" Job Content Questionnaire (5 for job demands and 9 for job control),[26] each item being assessed with a 5-point scale ranging from "strongly agree" to "strongly disagree". We dichotomized job demand and job control at the median to generate a job strain variable, high demand and low control signifying high job strain.

We used the PHQ-9 questionnaire to assess depressive symptoms.[27] It consists of nine items with a 4-point scale (0 to 3), ranging from 0 to 27. We defined mild to severe depressive symptoms according to the recommended cut-off value of ≥ 5.

Statistical Analysis

We dichotomized pain intensity at the highest tertile. We ran logistic regression models to study the associations of metabolic factors and adipokines with pain intensity controlling for age and gender. Within weight-related factors, lipids, other metabolic factors, adipokines, other lifestyle factors, and work-related factors we ran six additional age and gender adjusted models to identify the factors with a statistically significant association with pain intensity (family-wise analyses). We looked at a possible confounding effect of depressive symptoms with further adjustment in the final models. Stratified analyses were used to assess whether the effects of adipokines differed between overweight and non-overweight subjects. We used SPSS Statistics 20.0 software for the analysis.

RESULTS

Population characteristics

The subjects were on average 45 years old and predominantly female (Table 1). Fourteen per cent were obese using BMI as an indicator and 10% had high LDL cholesterol (>4.1 mmol/l). Thirty per cent had fasting glucose ≥5.6 mmol/l and 3% ≥7.0 mmol/l. Depressive symptoms were reported by 27% of the patients. Statin treatment was reported by 6% and antihypertensive medication by 15%. None of the patients used fibrate or nicotinic acid treatment. About half (52%) of the patients reported having used painkillers for their upper extremity problem, most of them irregularly. The mean pain intensity was 48. The cut-point for the highest tertile of pain intensity was 60. Subjects with shoulder disorders and epicondylitis each comprised about one third of the study population, and those with non-specific pain one fifth.

Metabolic factors and upper extremity pain

Obesity was associated with pain intensity (Table 2). The association was stronger with waist circumference or waist-to-hip ratio than with BMI. Subjects with low HDL cholesterol, high HDL ratio or high triglyceride levels reported high levels of pain intensity. Those with high job strain reported low pain intensity. The inverse association was partly explained by low waist circumference in those with high job strain (Two-tailed independent samples t-test p=0.007).

Fasting glucose, C-reactive protein, blood pressure, metabolic syndrome, leisure time physical exercise, smoking, alcohol consumption, fear avoidance beliefs and physical work load factors showed no associations with pain intensity.

Within weight-related factors waist circumference, within lipids HDL and triglycerides, within adipokines visfatin, and within the group of work-related factors job strain remained statistically significant in the family-wise analyses. In the final models, odds ratio of upper extremity pain was 3.2 (95% CI 1.3-7.9) for abdominal obesity, 4.1 (95% CI 1.5-11.0) for low HDL cholesterol, 3.0 (95% CI 1.2-7.6) for high triglycerides and 1.5 (95% CI 1.0-2.1) for one standard deviation increment of visfatin (Table 3). Further adjustment for depressive symptoms reduced the effects of abdominal obesity and triglycerides on pain intensity.

Waist circumference remained statistically significant with HDL in the model (OR 2.6, 95% CI 1.0-6.9 for abdominal obesity) but not when triglycerides were included in the model (OR 2.4, 95% CI 0.8-6.9). With waist circumference in the final model, OR was 3.2 (95% CI 1.1-9.0) for low HDL cholesterol and 2.3 (95% CI 0.8-6.8) for high triglycerides. The association between visfatin and upper extremity pain was similar in overweight and non-overweight subjects.

In a subanalysis including females and those not on statin or antihypertensive medication and adjusting for age, alcohol consumption and job strain, pain intensity was associated with obesity (OR 2.8, 95% CI 1.0-7.6), HDL cholesterol (OR 4.3, 95% CI 1.5-12.5 for low level), triglycerides (OR 2.6, 95% CI 1.0-7.0 for high level) and visfatin (OR 1.8, 95% CI 1.1-2.7 for one standard deviation increase in level). With waist circumference in

the final model, OR was 3.9 (95% CI 1.3-11.8) for low HDL cholesterol, 2.0 (95 % CI 0.7-6.3) for high triglycerides and 1.6 (95% CI 1.0-2.5) for visfatin.

DISCUSSION

Our study suggests independent associations of abdominal obesity and HDL with upper extremity pain in an inception cohort of patients with non-inflammatory upper extremity disorders. Moreover, of four studied adipokines (leptin, adiponectin, resistin, visfatin) only one (visfatin) was associated with upper extremity pain. Our findings support the role of abdominal obesity in upper extremity pain. Of obesity related indictors we looked at lipids, measures of glucose metabolism, a non-specific marker of inflammation and adipokines, however, our results did not clearly indicate any specific pathomechanical pathway.

The associations of weight related factors – especially abdominal obesity measured with waist circumference – point to a possible pain modulating role of abdominal fat in the early stage of UESTDs. Body fat indicators of body-composition did not show an association with upper extremity pain, probably because they do not measure abdominal obesity. The whole body bioimpedance technique is a valid method to estimate body fat percentage in normal or overweight subjects. In obese individuals (BMI ≥30) the accuracy is only moderate.[28] Therefore, waist circumference, as a traditional method of assessing abdominal fat accumulation, can be recommended for studies of UESTDs.

Serum lipids were associated with upper extremity pain, suggesting that they may have an independent role in soft-tissue pain modification at an early stage of UESTDs. We used data-driven cut-points to study the associations of HDL and triglycerides with pain, and the cut-points were lower for triglycerides and higher for HDL cholesterol than the clinical cut-points recommended by NCEP. Accordingly, our study showed associations

between lipids and upper extremity pain at lipid levels not considered to increase cardiovascular disease risk.

Adjusting for depressive symptoms decreased slightly the associations of obesity and lipids with pain intensity. Depressive symptoms and obesity are associated and the association seems to be bidirectional.[29] Moreover, depressive symptoms may precede pain or they can be a consequence of pain.[30 31] If depressive symptoms precede pain, unadjustment for depression will lead to an overestimation of the effects of obesity and lipids on pain. On the other hand, if depressive symptoms are a consequence of pain, adjustment for depression will lead to an underestimation of the effects of obesity and lipids on pain. Depressive people may have a higher perception of pain,[32 33] which would also lead to an overestimation of these associations.

In agreement with our study, some former studies have suggested an association of HDL with musculoskeletal pain.[34] Abdominal obesity, a major feature of the metabolic syndrome, is characteristically associated with systemic low-grade inflammation, as well as with both decreased HDL and increased triglycerides.[15 35] Increased synthesis of e.g. IL-1, a pivotal pro-inflammatory cytokine, may be a mediator in the pathomechanical pathway to increased pain intensity in UESTDs. Moreover, HDL has been shown to be an anti-atherogenic particle and an attenuator of vascular inflammation.[36] Therefore, HDL might also function as a pain modulator owing to its anti-inflammatory properties. Furthermore, increased triglycerides may function as an immunological metabolic stress signal, modifying pain through consecutive pro-inflammatory cascades [13 37]Finally, all these metabolic factors are involved in the pathomechanism of endothelial dysfunction and subsequent atherosclerosis. [15]

Of the adipokines studied, a high level of circulating visfatin was linked with upper extremity pain. Previous studies of rheumatoid arthritis and osteoarthritis have shown resistin and visfatin expression linking with disease activity,[38 39 40] suggesting indirectly a relationship between adipokines and pain in these conditions. Visfatin is a metabolically active insulin imitator secreted by white adipose tissue and expressed increasingly by fat accumulation. In contrast, in humans other cell types than adipocytes mostly synthesise resistin, such as mononuclear and endothelial cells, unrelated with fat mass. Both resistin and visfatin are pro-inflammatory stimulating for example IL-1 and IL-6 expression that have distinct effects on the musculoskeletal system. In osteoarthritis, for instance, cartilage damage signalling occurs partly by cytokines such as IL-6. In UESTDs, these pro-inflammatory proteins may participate also in pain signalling in cooperation with adipokines. Furthermore, adipokines and lipids may have parallel inflammatory pain signalling pathways in UESTDs.

In conclusion, obesity, especially abdominal obesity and lipids may have an impact on pain intensity in UESTD. They may intensify pain through proinflammatory pain-modifying molecular pathways or by causing soft tissue pathology and dysfunction of their supplying arteries. Of four adipokines studied only one (visfatin) was associated with pain intensity. In the future, further studies are required to better understand the relationship between metabolic factors and UESTDs.

Contributors

Martti Rechardt was involved in data acquisition, data analysis and interpretation and manuscript drafting. Rahman Shiri was involved in data analysis and interpretation and manuscript drafting. Harri Lindholm was involved in data analysis and interpretation and critically revised the manuscript. Jaro Karppinen was involved in conception and design of the study, data analysis and interpretation and critically revised the manuscript. Eira Viikari-Juntura was in charge of the conception and design of the study, and was involved in data analysis and interpretation and manuscript drafting. All authors approved the final manuscript.

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Competing interests

The authors declare that they have no conflicts of interest.

Data sharing

The current ethical approval does not allow to share the data for public scientific use. In case the manuscript will be accepted we will ask the Coordinating Ethics Committee of Hospital District of Helsinki and Uusimaa in Finland for permission.

Thereafter, the dataset may be available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset.

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Table 1
Characteristics of the study population (N=163), percentage (%) and 95% confidence interval (CI) or mean (SD).

Characteristic	%	95% CI	Mean	SD
Age (years)			45.0	9.8
Males	14			
Body mass index (kg/m^2)			25.5	4.3
Waist circumference (cm)			83.4	12.7
Waist-to-hip ratio			0.83	0.08
Fat percent			27.2	8.0
Body fat index (kg/m^2)			6.6	3.9
Total cholesterol (mmol/l)			5.1	0.9
LDL cholesterol (mmol/l)			2.9	0.8
HDL cholesterol (mmol/l)			1.7	0.5
Triglycerides (mmol/l)			1.1	0.6
Fasting glucose (mmol/l)			5.3	0.9
High CRP (≥ 3.0 mg/ml)	18	12-24		
Systolic blood pressure (mmHg)			124	17
Diastolic blood pressure (mmHg)			82	11
Adipokines				
Adiponectin (pg/l)			3444	1553
Leptin (pg/l)			14762	12375
Resistin (pg/l)			14662	4481
Visfatin (ng/l)			1.1	0.6
Metabolic syndrome	18	12-24		
Current smoking	11	6-16		
Alcohol consumption ≥ 2 times per week	19	13-25		
Physical exercise ≥ 3 times per week	51	43-59		
High physical load	37	30-45		
High fear avoidance beliefs score	13	7-18		
High job strain	26	19-33		
Depressive symptoms	27	20-33		
Medication				
Statin	6	2-9		
Antihypertensive	15	9-20		
Antidiabetic	1	0-3		
Antidepressive	4	1-7		
Pain intensity (0-100)			48	22
Diagnostic subgroups				
Shoulder disorder	36	28-43		
Epicondylitis	31	24-38		
Wrist tendinitis or carpal tunnel syndrome	13	8-18		
Non-specific pain	20	14-26		

Table 2
Age and gender adjusted odd ratios (OR) of pain intensity according to metabolic factors, adipokines, medication, depressive symptoms and work-related factors.

Characteristic	OR	95% CI
Body mass index (kg/m^2)		
<25.0	1	
25.0–29.9	1.9	0.9-4.0
≥30.0	2.1	0.8-5.4
Waist circumference[a]		
Normal	1	
Overweight	1.6	0.6-3.8
Obese	3.2	1.4-7.4
Waist-hip-ratio[b]		
Normal	1	
Overweight	1.0	0.5-2.2
Obese	3.3	1.3-8.6
Fat percent tertile		
<23.3	1	
23.3-30.5	0.9	0.3-2.3
>30.5	1.7	0.7-4.2
Body fat index tertile (kg/m^2)		
<5.13	1	
5.13-7.41	0.9	0.4-2.3
>7.41	1.6	0.7-3.6
Total cholesterol tertile (mmol/l)		
<4.7	1	
4.7-5.3	1.0	0.4-2.7
>5.3	1.8	0.8-4.0
LDL cholesterol tertile (mmol/l)		
<2.5	1	
2.5-3.3	1.1	0.4-2.6
>3.3	1.7	0.7-4.2
HDL cholesterol tertile (mmol/l)		
>1.83	1	
1..48-1.83	0.9	0.4-2.2
<1.48	2.7	1.2-6.3
HDL ratio tertile		
<2.73	1	
2.73–3.31	2.8	1.2-6.9
>3.31	2.6	1.1-6.4
Triglycerides tertile (mmol/l)		
<0.72	1	
0.72–1.08	1.7	0.7-4.0
>1.08	2.8	1.2-6.6
Adipokines[c]		
Adiponectin	0.9	0.6-1.3
Leptin	1.2	0.9-1.8
Resistin	1.2	0.8-1.6
Visfatin	1.4	1.0-2.0
Medication		
Statin	0.9	0.2-4.3
Antihypertensive	1.5	0.6-3.8
Antidepressive	1.2	0.2-7.6
Depressive symptoms	2.5	1.2-5.2
Physical load	1.5	0.7-3.1
Job Strain	0.2	0.1-0.7
Fear avoidance beliefs	1.2	0.4-3.4

[a] Normal: Men <94 cm, Women <80 cm; Overweight Men 94-101.9 cm, Women 80-87.9 cm; Obese Men ≥102 cm, Women ≥88 cm.
[b] Normal: Men <0.9, Women <0.8; Overweight: Men 0.9-1.0; Obese: Women 0.8-0.9 Men >1.0; Women >0.9.
[c] Continuous variable; increment of one SD

Table 3
The associations of obesity, lipids and adipokines with upper extremity pain intensity

	OR[c]	95% CI	OR[d]	95% CI
Waist circumference [a]				
Normal	1		1	
Overweight	1.2	0.5-3.2	1.2	0.4-3.2
Obese	3.2	1.3-7.9	2.9	1.1-7.3
HDL cholesterol tertile (mmol/l)				
>1.83	1		1	
1.48–1.83	0.8	0.3-2.2	0.7	0.2-2.0
<1.48	4.1	1.5-11.0	3.9	1.4-10.1
Triglycerides tertile (mmol/l)				
<0.72	1		1	
0.72–1.08	1.6	0.6-4.1	1.4	0.5-3.8
>1.08	3.0	1.2-7.6	2.6	1.0-6.8
Visfatin[b]	1.5	1.0-2.1	1.4	1.0-2.1

[a] Normal: Men <94 cm, Women <80 cm; Overweight: Men 94-101.9 cm , Women 80-87.9 cm; Obese: Men ≥102 cm, Women ≥88 cm.
[b] Continuous variable; increment of one SD
[c] Adjusted for age, gender, statin medication, alcohol consumption and job strain.
[d] Further adjustment for depressive symptoms

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-11
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	13
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Table 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 and p.12
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1 and p. 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, 3
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Associations of metabolic factors and adipokines with pain in incipient upper extremity soft tissue disorders: A cross-sectional study

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The associations of metabolic factors and adipokines with pain in incipient upper extremity soft tissue disorders: a cross-sectional study

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ABSTRACT

Objectives: Earlier studies have suggested associations between metabolic factors and musculoskeletal pain or disorders. We studied the associations of obesity, lipids, other features of the metabolic syndrome and adipokines (adiponectin, leptin, resistin, visfatin) with upper extremity pain in a clinical population with incipient upper extremity soft tissue disorders (UESTDs).

Design: A cross-sectional study.

Setting: Primary health care (occupational health service) with further examinations at a research institute.

Participants: Patients (N=163, 86% were women) seeking medical advice in the occupational health service due to incipient upper extremity symptoms with symptom duration of less than one month were referred for consultation to the Finnish Institute of Occupational Health from spring 2006 to fall 2008. We included all actively working subjects meeting diagnostic criteria based on physical examination. We excluded subjects meeting predetermined conditions.

Outcome measure: Pain intensity was assessed with visual analogue scale and dichotomized at the highest tertile (cut-point 60).

Results: Obesity (adjusted odds ratio (OR) for high waist circumference 2.9, 95% CI 1.1-7.3), HDL cholesterol (OR 3.9, 95% CI 1.4-10.1 for low level) and triglycerides (OR 2.6, 95% CI 1.0-6.8 for high level) were associated with pain intensity. Of four adipokines studied, only visfatin was associated with upper extremity pain (adjusted OR 1.4, 95% CI 1.0-2.1 for one standard deviation increase in level).

Conclusions: Abdominal obesity and lipids may have an impact on pain intensity in UESTDs. They may intensify pain through proinflammatory pain-modifying molecular pathways or by causing soft tissue pathology and dysfunction of their supplying arteries. Of four adipokines studied only one (visfatin) was associated with pain intensity. In the

future, further studies are required to better understand the relationship between metabolic factors and UESTDs.

ARTICLE SUMMARY

Article focus:

- We studied the associations of metabolic factors, serum C-reactive protein and adipokines with upper extremity pain intensity among subjects with incipient upper extremity soft tissue disorders (UESTDs).

Key messages:

- Subjects with abdominal obesity, low level of high-density lipoprotein (HDL) cholesterol, high level of triglycerides or high level of the adipokine visfatin reported higher upper extremity pain intensity than those with normal waist circumference, higher level of HDL cholesterol, normal level of triglycerides, or low level of visfatin.
- Further studies are needed to understand the role of metabolic factors in UESTDs.

Strengths and limitations of the study:

- Strengths of the study include: 1) Metabolic factors and adipokines were measured, and 2) Patients with early stage of upper extremity soft tissue disorders were included in the study.
- Limitations of the study include: 1) Small sample size, 2) Cross sectional design of the study.

INTRODUCTION

Upper extremity pain is a common health problem in general populations. The prevalence of forearm pain during the preceding 30 days has been estimated at 8%, [1] and that of shoulder pain has ranged between 12% and 30%.[1-4] In the general population, one of five persons reports chronic upper extremity pain.[5] Common causes for upper extremity pain include soft tissue disorders, such as rotator cuff tendinitis, epicondylitis and tenosynovitis.[6]

Some studies have suggested an association between musculoskeletal pain or disorders and metabolic factors, such as obesity, lipids and hyperglycaemia.[7-9] In a French working population study, obese men and diabetic women had a significantly higher occurrence of upper extremity soft tissue disorders (UESTDs, mostly comprising of tendon disorders) compared with subjects without such metabolic disorders.[10] In addition, an association has been reported between carpal tunnel syndrome and serum lipids. [11 12]

Obesity is often an underlying factor for dyslipidemia and disturbances of glucose metabolism. It may cause a systemic low grade inflammation and increased pro-inflammatory activity with elevated cytokine levels.[13] Dyslipidemia may cause accumulation of lipids on musculoskeletal structures, e.g., tendons.[11 12] Advanced glycation end-products may accumulate in hyperglycaemia resulting in latent collagen and microvascular alterations.[13 14]

Adipokines are proteins largely released by adipocytes, typically showing increased production in obesity. Characteristically, they exert widespread effects on immunological processes for example by stimulating cytokine expression. Adipokines function also in musculoskeletal disorders, best documented in degenerative inflammatory joint

conditions.[15] We are not aware of studies on the role of adipokines in non-inflammatory upper extremity disorders.

We studied the associations of obesity, lipids, other features of the metabolic syndrome and adipokines with upper extremity pain in a clinical population with incipient UESTDs. We hypothesised that UESTD patients with obesity, dyslipidemia, high C-reactive protein and adipokines report higher levels of pain intensity than patients without these risk factors. Furthermore, we explored whether the associations of adipokines with upper extremity pain differ in overweight and non-overweight subjects.

METHODS

Patients

This cross-sectional study was a part of a larger project on metabolic and inflammatory factors in UESTDs. Included conditions were shoulder disorders, e.g., rotator cuff tendinitis, elbow disorders, e.g., humeral epicondylitis, and wrist disorders, e.g., tenosynovitis. Between spring 2006 and fall 2008, three occupational health care units in Helsinki referred all eligible patients seeking medical advice for incipient upper extremity pain with symptom duration of less than one month to the Finnish Institute of Occupational Health for further examinations. In the final study population we included all actively working subjects meeting diagnostic criteria based on physical examination.[16]

We excluded patients whose main problem was a spine or cervical disorder, advanced osteoarthritis, autoimmune disease, fibromyalgia, malignancy, history of recent injury, former surgery related to the current problem, and presence of deformity. We also excluded 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.

Ethics Statement

The Coordinating Ethical Committee of Helsinki University Hospital District has approved this study on 16th of August 2006. All subjects signed an informed consent form before entering the study.

Outcome

Symptoms were determined by the examining physician. A standardized protocol was used that included symptom questions and clinical tests. A visual analogue scale was used to assess pain intensity during the preceding week (0=no pain, 100= highest pain intensity possible). Pain intensity was dichotomized at the highest tertile (cut-point 60).

Independent Variables

We measured body height and weight, and systolic and diastolic blood pressure with standard procedures. Waist circumference was measured halfway between the lowest rib and iliac crest, and hip circumference was measured at the trochanter level. We calculated body mass index (BMI) as body weight in kilograms / (height in meters)^2. The subjects were categorized according to BMI into underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9) and obese (BMI ≥30.0).[17] Waist circumference was grouped into three levels; in men < 94.0 cm, 94.0-101.9 cm, ≥102.0 cm and in women <80.0 cm, 80.0-87.9 cm and ≥88.0 cm.[17] Waist-to-hip ratio was calculated as a ratio of waist circumference and hip circumference and classified into three groups: in men <0.9, 0.9-1.0, >1.0 and in women <0.8, 0.8-0.9 and >0.9.[17 18] Body fat was measured with the whole body bioimpedance technique (InBody 720, South-Chorea). We calculated body fat index as total body fat mass in kilograms / (height in meters)^2. In addition, we inquired the use of regular drug treatment.

Fasting blood samples were analysed with Advia 1800® (Siemens Healthcare Diagnostics, USA) for serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and blood glucose as well as serum C-reactive protein (CRP). For lipids we applied clinical cut points recommended by the National

Cholesterol Education Program (NCEP) of the National Institutes of Health.[19] We stratified lipid variables in tertiles in case the NCEP cut-points resulted in too small subgroups. Fasting glucose was stratified in tertiles. To identify the metabolic syndrome we used the revised NCEP classification,[20] requiring at least 3 of the following findings: 1) central obesity, defined as waist circumference ≥ 102 cm in men and ≥88 cm in women; 2) high fasting triglycerides, defined as ≥ 1.7 mmol/l (> 150 mg/dL) or drug treatment for elevated triglycerides; 3) low HDL cholesterol defined as < 1.0 mmol/l in men (< 40 mg/dL) and < 1.3 mmol/l (< 50 mg/dL) in women or drug treatment for reduced HDL; 4) elevated blood pressure, defined as 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, defined as fasting glucose ≥ 5.6 mmol/l (100 mg/dL) or drug treatment for elevated glucose.

High CRP was defined as ≥ 3.0 mg/l.[21] Serum leptin, adiponectin, resistin (DuoSet ELISA R&D systems) and visfatin (Human Visfatin ELISA Kit, AdipoGen) were determined with enzyme-linked immunosorbent assay kits according to the manufacturer's instructions. Adipokines were used as continuous variables and their associations were modeled for one standard deviation increase in their level.

Smoking was classified as never, former, occasional or current. Alcohol consumption was determined as frequency of drinking alcohol per time unit, categorized into none or ≤1 times per month, 2-4 times per month, or ≥2 times per week. Physical exercise was defined as the number of sessions per week of physical activities for at least 30 minutes causing sweating or shortness of breath and categorized into none or sometimes, 1-2, 3-4, or ≥5 times per week.

Exposure to physical load factors was assessed with an interview by a physician. The patients were inquired 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 deviated wrist posture, and the use of vibrating tools. Each factor was dichotomized using a cut-off point of being exposed for ≥10% of the work time during a workday.

We assessed fear-avoidance beliefs with the 4-item Physical Activity subscale of the Fear-Avoidance Beliefs Questionnaire:[22] "physical activity makes my symptoms worse"; "if my symptoms become worse, it means that I should stop what I was doing"; "my pain is caused by work"; and "I should not continue in my present job because of the symptoms". Each item had a 7-point scale from "totally disagree" to "totally agree". We defined fear-avoidance beliefs as high when the score was ≥18 (of maximum of 24).

We evaluated job strain using the "14 item" Job Content Questionnaire (5 for job demands and 9 for job control),[23] each item being assessed with a 5-point scale ranging from "strongly agree" to "strongly disagree". We dichotomized job demand and job control at the median to generate a job strain variable, high demand and low control signifying high job strain.

We used the PHQ-9 questionnaire to assess depressive symptoms.[24] It consists of nine items with a 4-point scale (0 to 3), ranging from 0 to 27. We defined mild to severe depressive symptoms according to the recommended cut-off value of ≥ 5.

Statistical Analysis

We dichotomized pain intensity at the highest tertile. We ran logistic regression models to study the associations of metabolic factors and adipokines with pain intensity controlling for age and gender. Because of small sample size, we first ran age- and gender-adjusted regression analyses to identify significant covariates within each family of independent variables. We grouped the independent variables into six families and ran six age- and gender-adjusted regression analyses for 1) weight-related factors (BMI, waist circumference and waist-hip ratio); 2) lipids (total cholesterol, LDL-cholesterol, HDL cholesterol, HDL ratio and triglycerides); 3) other metabolic factors (fasting glucose, systolic and diastolic blood pressure and metabolic syndrome); 4) adipokines; 5) other lifestyle factors (smoking, alcohol consumption and physical exercise) and 6) work-related factors (physical load and job strain).. We looked at a possible confounding effect of depressive symptoms with further adjustment in the final models. Stratified analyses were carried out to assess whether the effects of adipokines differed between overweight and non-overweight subjects. We used SPSS Statistics 20.0 software for the analysis.

RESULTS

Population characteristics

The subjects were on average 45 years old and predominantly female (Table 1). Fourteen per cent were obese using BMI as an indicator and 10% had high LDL cholesterol (>4.1 mmol/l). Thirty per cent had fasting glucose ≥5.6 mmol/l and 3% ≥7.0 mmol/l. Depressive symptoms were reported by 27% of the patients. Statin treatment was reported by 6% and antihypertensive medication by 15%. None of the patients used fibrate or nicotinic acid treatment. About half (52%) of the patients reported having used painkillers for their upper extremity problem, most of them irregularly. The mean pain intensity was 48. The cut-point for the highest tertile of pain intensity was 60. Subjects with shoulder disorders and epicondylitis each comprised about one third of the study population, and those with non-specific pain one fifth.

Metabolic factors and upper extremity pain

Obesity was associated with pain intensity (Table 2). The association was stronger with waist circumference or waist-to-hip ratio than with BMI. Subjects with low HDL cholesterol, high HDL ratio or high triglyceride levels reported high levels of pain intensity. Those with high job strain reported low pain intensity. The inverse association was partly explained by low waist circumference in those with high job strain (Two-tailed independent samples t-test p=0.007). However, the association between job strain and pain intensity remained statistically significant after further adjustment for waist circumference. Odds ratio of pain intensity for high job strain was 0.3 (0.1-0.9) after adjustment for age, gender and waist circumference.

Fasting glucose, C-reactive protein, blood pressure, metabolic syndrome, leisure time physical exercise, smoking, alcohol consumption, fear avoidance beliefs and physical work load factors showed no associations with pain intensity.

Within weight-related factors waist circumference, within lipids HDL and triglycerides, within adipokines visfatin, and within the group of work-related factors job strain remained statistically significant in the family-wise analyses. In the final models, odds ratio of upper extremity pain was 3.2 (95% CI 1.3-7.9) for abdominal obesity, 4.1 (95% CI 1.5-11.0) for low HDL cholesterol, 3.0 (95% CI 1.2-7.6) for high triglycerides and 1.5 (95% CI 1.0-2.1) for one standard deviation increment of visfatin (Table 3). Further adjustment for depressive symptoms reduced the effects of abdominal obesity and triglycerides on pain intensity.

Waist circumference remained statistically significant with HDL in the model (OR 2.6, 95% CI 1.0-6.9 for abdominal obesity) but not when triglycerides were included in the model (OR 2.4, 95% CI 0.8-6.9). With waist circumference in the final model, OR was 3.2 (95% CI 1.1-9.0) for low HDL cholesterol and 2.3 (95% CI 0.8-6.8) for high triglycerides. The association between visfatin and upper extremity pain was similar in overweight and non-overweight subjects. Odds ratio of pain intensity for visfatin was 1.8 (95% CI 0.6-5.1) among non-overweight subjects and 2.0 (95% CI 0.8-4.6) among overweight/obese subjects.

In a subanalysis including females not on statin or antihypertensive medication and adjusting for age, alcohol consumption and job strain, pain intensity was associated with obesity (OR 2.8, 95% CI 1.0-7.6), HDL cholesterol (OR 4.3, 95% CI 1.5-12.5 for low level), triglycerides (OR 2.6, 95% CI 1.0-7.0 for high level) and visfatin (OR 1.8, 95% CI 1.1-2.7 for one standard deviation increase in level). With waist circumference in the final

model, OR was 3.9 (95% CI 1.3-11.8) for low HDL cholesterol, 2.0 (95 % CI 0.7-6.3) for high triglycerides and 1.6 (95% CI 1.0-2.5) for visfatin.

DISCUSSION

Our study suggests independent associations of abdominal obesity and HDL with upper extremity pain in an inception cohort of patients with non-inflammatory upper extremity disorders. Moreover, of four studied adipokines (leptin, adiponectin, resistin, visfatin) only one (visfatin) was associated with upper extremity pain. Our findings support the role of abdominal obesity in upper extremity pain. Of obesity related indictors we looked at lipids, measures of glucose metabolism, a non-specific marker of inflammation and adipokines, however, our results did not clearly indicate any specific pathomechanical pathway.

We studied three commonly occurring specific soft-tissue disorders of the upper extremity: shoulder disorders (most typically shoulder tendinitis or shoulder impingement syndrome), epicondylitis and tenosynovitis of the wrist. Previous studies have found associations between metabolic factors and these disorders. [9 10] Metabolic factors, such as obesity and lipids have been associated also with carpal tunnel syndrome. [11 12] Moreover, carpal tunnel syndrome may be a result of wrist flexor tenosynovitis.

The associations of weight related factors – especially abdominal obesity measured with waist circumference – point to a possible pain modulating role of abdominal fat in the early stage of UESTDs. Body fat indicators of body-composition did not show an association with upper extremity pain, probably because they do not measure abdominal obesity. The whole body bioimpedance technique is a valid method to estimate body fat percentage in normal or overweight subjects. In obese individuals (BMI ≥30) the accuracy is only moderate.[25] Therefore, waist circumference, as a traditional method of assessing abdominal fat accumulation, can be recommended for studies of UESTDs.

Serum lipids were associated with upper extremity pain, suggesting that they may have an independent role in soft-tissue pain modification at an early stage of UESTDs. We used data-driven cut-points to study the associations of HDL and triglycerides with pain, and the cut-points were lower for triglycerides and higher for HDL cholesterol than the clinical cut-points recommended by NCEP. Only the lowest tertile of HDL cholesterol and the highest tertile of triglycerides were associated with pain intensity.

Adjusting for depressive symptoms decreased slightly the associations of obesity and lipids with pain intensity. Depressive symptoms and obesity are associated and the association seems to be bidirectional.[26] Moreover, depressive symptoms may precede pain or they can be a consequence of pain.[27 28] If depressive symptoms precede pain, not adjusting for depression will lead to an overestimation of the effects of obesity and lipids on pain. On the other hand, if depressive symptoms are a consequence of pain, adjustment for depression will lead to an underestimation of the effects of obesity and lipids on pain. Depressive people may have a higher perception of pain,[29 30] which would also lead to an overestimation of these associations.

In agreement with our study, some former studies have suggested an association of HDL with musculoskeletal pain.[31] Abdominal obesity, a major feature of the metabolic syndrome, is characteristically associated with systemic low-grade inflammation, as well as with both decreased HDL and increased triglycerides.[12 32] Increased synthesis of e.g. IL-1, a pivotal pro-inflammatory cytokine, may be a mediator in the pathomechanical pathway to increased pain intensity in UESTDs. Moreover, HDL has been shown to be an anti-atherogenic particle and an attenuator of vascular inflammation.[33] Therefore, HDL might also function as a pain modulator owing to its anti-inflammatory properties. Furthermore, increased triglycerides may function as an immunological metabolic stress signal, modifying pain through consecutive pro-inflammatory cascades [34 35]Finally, all

these metabolic factors are involved in the pathomechanism of endothelial dysfunction and subsequent atherosclerosis. [12]

Of the adipokines studied, a high level of circulating visfatin was linked with upper extremity pain. Previous studies of rheumatoid arthritis and osteoarthritis have shown resistin and visfatin expression linking with disease activity,[36 37 38] suggesting indirectly a relationship between adipokines and pain in these conditions. Visfatin is a metabolically active insulin imitator secreted by white adipose tissue and expressed increasingly by fat accumulation. In contrast, in humans other cell types than adipocytes mostly synthesise resistin, such as mononuclear and endothelial cells, unrelated with fat mass. Both resistin and visfatin are pro-inflammatory stimulating for example IL-1 and IL-6 expression that have distinct effects on the musculoskeletal system. In osteoarthritis, for instance, cartilage damage signalling occurs partly by cytokines such as IL-6. In UESTDs, these pro-inflammatory proteins may participate also in pain signalling in cooperation with adipokines. Furthermore, adipokines and lipids may have parallel inflammatory pain signalling pathways in UESTDs.

The population of the current study was predominantly women due to the workplace settings in question such as a central hospital. Due to the small number of men we could not run appropriate regression analyses to see whether the associations found among women were similar in men. Therefore, the findings of this study can be generalized to women only. Moreover, due to cross-sectional nature of the current study causal inference cannot be made.

In conclusion, obesity, especially abdominal obesity and lipids may have an impact on pain intensity in UESTD. They may intensify pain through proinflammatory pain-modifying molecular pathways or by causing soft tissue pathology and dysfunction of their supplying arteries. Of four adipokines studied only one (visfatin) was associated

with pain intensity. In the future, further studies are required to better understand the relationship between metabolic factors and UESTDs.

Contributors

Martti Rechardt was involved in data acquisition, data analysis and interpretation and manuscript drafting. Rahman Shiri was involved in data analysis and interpretation and manuscript drafting. Harri Lindholm was involved in data analysis and interpretation and critically revised the manuscript. Jaro Karppinen was involved in conception and design of the study, data analysis and interpretation and critically revised the manuscript. Eira Viikari-Juntura was in charge of the conception and design of the study, and was involved in data analysis and interpretation and manuscript drafting. All authors approved the final manuscript.

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Competing interests

The authors declare that they have no conflicts of interest.

Patient consent

Each patient gave an informed consent for the study.

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Table 1
Characteristics of the study population (N=163), percentage (%)or mean (SD).

Characteristic	%	Mean	SD
Age (years)		45.0	9.8
Males	14		
Body mass index (kg/m^2)		25.5	4.3
Waist circumference (cm)		83.4	12.7
Waist-to-hip ratio		0.83	0.08
Fat percent		27.2	8.0
Body fat index (kg/m^2)		6.6	3.9
Total cholesterol (mmol/l)		5.1	0.9
LDL cholesterol (mmol/l)		2.9	0.8
HDL cholesterol (mmol/l)		1.7	0.5
Triglycerides (mmol/l)		1.1	0.6
Fasting glucose (mmol/l)		5.3	0.9
High CRP (≥ 3.0 mg/ml)	18		
Systolic blood pressure (mmHg)		124	17
Diastolic blood pressure (mmHg)		82	11
Adipokines			
Adiponectin (pg/l)		3444	1553
Leptin (pg/l)		14762	12375
Resistin (pg/l)		14662	4481
Visfatin (ng/l)		1.1	0.6
Metabolic syndrome	18		
Current smoking	11		
Alcohol consumption ≥ 2 times per week	19		
Physical exercise ≥ 3 times per week	51		
High physical load	37		
High fear avoidance beliefs score	13		
High job strain	26		
Depressive symptoms	27		
Medication			
Statin	6		
Antihypertensive	15		
Antidiabetic	1		
Antidepressive	4		
Pain intensity (0-100)		48	22
Diagnostic subgroups			
Shoulder disorder	36		
Epicondylitis	31		
Wrist tendinitis or carpal tunnel syndrome	13		
Non-specific pain	20		

Table 2
Age and gender adjusted odd ratios (OR) of pain intensity according to metabolic factors, adipokines, medication, depressive symptoms and work-related factors.

Characteristic	OR	95% CI
Body mass index (kg/m^2)		
<25.0	1	
25.0–29.9	1.9	0.9-4.0
≥30.0	2.1	0.8-5.4
Waist circumference[a]		
Normal	1	
Overweight	1.6	0.6-3.8
Obese	3.2	1.4-7.4
Waist-hip-ratio[b]		
Normal	1	
Overweight	1.0	0.5-2.2
Obese	3.3	1.3-8.6
Fat percent tertile		
<23.3	1	
23.3-30.5	0.9	0.3-2.3
>30.5	1.7	0.7-4.2
Body fat index tertile (kg/m^2)		
<5.13	1	
5.13-7.41	0.9	0.4-2.3
>7.41	1.6	0.7-3.6
Total cholesterol tertile (mmol/l)		
<4.7	1	
4.7-5.3	1.0	0.4-2.7
>5.3	1.8	0.8-4.0
LDL cholesterol tertile (mmol/l)		
<2.5	1	
2.5-3.3	1.1	0.4-2.6
>3.3	1.7	0.7-4.2
HDL cholesterol tertile (mmol/l)		
>1.83	1	
1..48-1.83	0.9	0.4-2.2
<1.48	2.7	1.2-6.3
HDL ratio tertile		
<2.73	1	
2.73–3.31	2.8	1.2-6.9
>3.31	2.6	1.1-6.4
Triglycerides tertile (mmol/l)		
<0.72	1	
0.72–1.08	1.7	0.7-4.0
>1.08	2.8	1.2-6.6
Adipokines[c]		
Adiponectin	0.9	0.6-1.3
Leptin	1.2	0.9-1.8
Resistin	1.2	0.8-1.6
Visfatin	1.4	1.0-2.0
Medication		
Statin	0.9	0.2-4.3
Antihypertensive	1.5	0.6-3.8
Antidepressive	1.2	0.2-7.6
Depressive symptoms	2.5	1.2-5.2
Physical load	1.5	0.7-3.1
Job Strain	0.2	0.1-0.7
Fear avoidance beliefs	1.2	0.4-3.4

[a] Normal: Men <94 cm, Women <80 cm; Overweight Men 94-101.9 cm, Women 80-87.9 cm; Obese Men ≥102 cm, Women ≥88 cm.
[b] Normal: Men <0.9, Women <0.8; Overweight: Men 0.9-1.0; Obese: Women 0.8-0.9 Men >1.0; Women >0.9.
[c] Continuous variable; increment of one SD

Table 3
The associations of obesity, lipids and adipokines with upper extremity pain intensity

	OR[c]	95% CI	OR[d]	95% CI
Waist circumference [a]				
Normal	1		1	
Overweight	1.2	0.5-3.2	1.2	0.4-3.2
Obese	3.2	1.3-7.9	2.9	1.1-7.3
HDL cholesterol tertile (mmol/l)				
>1.83	1		1	
1.48–1.83	0.8	0.3-2.2	0.7	0.2-2.0
<1.48	4.1	1.5-11.0	3.9	1.4-10.1
Triglycerides tertile (mmol/l)				
<0.72	1		1	
0.72–1.08	1.6	0.6-4.1	1.4	0.5-3.8
>1.08	3.0	1.2-7.6	2.6	1.0-6.8
Visfatin[b]	1.5	1.0-2.1	1.4	1.0-2.1

[a] Normal: Men <94 cm, Women <80 cm; Overweight: Men 94-101.9 cm , Women 80-87.9 cm; Obese: Men ≥102 cm, Women ≥88 cm.
[b] Continuous variable; increment of one SD
[c] Adjusted for age, gender, statin medication, alcohol consumption and job strain.
[d] Further adjustment for depressive symptoms

The associations of metabolic factors and adipokines with pain in incipient upper extremity soft tissue disorders: a cross-sectional study

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ABSTRACT

Objectives: Earlier studies have suggested associations between metabolic factors and musculoskeletal pain or disorders. –We studied the associations of obesity, lipids, other features of the metabolic syndrome and adipokines (adiponectin, leptin, resistin, visfatin) with upper extremity pain in a clinical population with incipient upper extremity soft tissue disorders (UESTDs).

Design: A cross-sectional study.

Setting: Primary health care (occupational health service) with further examinations at a research institute.

Participants: Patients (N=163, 86% were women) seeking medical advice in the occupational health service due to incipient upper extremity symptoms with symptom duration of less than one month were referred for consultation to the Finnish Institute of Occupational Health from spring 2006 to fall 2008. We included all actively working subjects meeting diagnostic criteria based on physical examination. We excluded subjects meeting predetermined conditions.

Outcome measure: Pain intensity was assessed with visual analogue scale and dichotomized at the highest tertile (cut-point 60).

Results: Obesity (adjusted odds ratio (OR) for high waist circumference 2.9, 95% CI 1.1-7.3), HDL cholesterol (OR 3.9, 95% CI 1.4-10.1 for low level) and triglycerides (OR 2.6, 95% CI 1.0-6.8 for high level) were associated with pain intensity. Of four adipokines studied, only visfatin was associated with upper extremity pain (adjusted OR 1.4, 95% CI 1.0-2.1 for one standard deviation increase in level).

Conclusions: Abdominal obesity and lipids may have an impact on pain intensity in UESTDs. They may intensify pain through proinflammatory pain-modifying molecular pathways or by causing soft tissue pathology and dysfunction of their supplying arteries. Of four adipokines studied only one (visfatin) was associated with pain intensity. In the

future, further studies are required to better understand the relationship between metabolic factors and UESTDs.

ARTICLE SUMMARY

Article focus:

- We studied the associations of metabolic factors, serum C-reactive protein and adipokines with upper extremity pain intensity among subjects with incipient upper extremity soft tissue disorders (UESTDs).

Key messages:

- Subjects with abdominal obesity, low levels of high-density lipoprotein (HDL) cholesterol, high level of triglycerides or high levels of the adipokine visfatin reported higher upper extremity pain intensity than those with normal waist circumference, higher levels of HDL cholesterol, normal level of triglycerides, or low levels of visfatin.
- Further studies are needed to understand the role of metabolic factors in UESTDs.

Strengths and limitations of the study:

- Strengths of the study include: 1) Metabolic factors and adipokines were measured, and 2) Patients with early stage of upper extremity soft tissue disorders were included in the study.
- Limitations of the study include: 1) Small sample size, 2) Cross sectional design of the study.

INTRODUCTION

Upper extremity pain is a common health problem in general populations. The prevalence of forearm pain during the preceding 30 days has been estimated at 8%, [1] and that of shoulder pain has ranged between 12% and 30%.[1-4] In the general population, one of five persons reports chronic upper extremity pain.[5] Common causes for upper extremity pain include soft tissue disorders, such as rotator cuff tendinitis, epicondylitis and tenosynovitis.[6]

Some studies have suggested an association between musculoskeletal pain or disorders and metabolic factors, such as obesity, lipids and hyperglycaemia.[7-9] In a French working population study, obese men and diabetic women had a significantly higher occurrence of upper extremity soft tissue disorders (UESTDs~~)~~, mostly comprising of tendon disorders) compared ~~to~~ with subjects without such metabolic disorders.[10] In addition, an association has been reported between carpal tunnel syndrome and serum lipids.[11 12]

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Obesity is often an underlying factor for dyslipidemia and disturbances of glucose metabolism. It may cause a systemic low grade inflammation and increased pro-inflammatory activity with elevated cytokine levels.[13] Dyslipidemia may cause accumulation of lipids on musculoskeletal structures, e.g., tendons.[11 12] Advanced glycation end-products may accumulate in hyperglycaemia resulting in latent collagen and microvascular alterations.[13 14]

Adipokines are proteins largely released by adipocytes, typically showing increased production in obesity. Characteristically, they exert widespread effects on immunological processes for example by stimulating cytokine expression. Adipokines function also in musculoskeletal disorders, best documented in degenerative inflammatory joint

conditions.[15] We are not aware of studies on the role of adipokines in non-inflammatory upper extremity disorders.

We studied the associations of obesity, lipids, other features of the metabolic syndrome and adipokines with upper extremity pain in a clinical population with incipient UESTDs. We hypothesised that UESTD patients with obesity, dyslipidemia, high C-reactive protein and adipokines report higher levels of pain intensity than patients without these risk factors. Furthermore, we explored whether the associations of adipokines with upper extremity pain differ in overweight and non-overweight subjects.

METHODS

Patients

This cross-sectional study was a part of a larger project on metabolic and inflammatory factors in UESTDs. Included conditions were shoulder disorders, e.g., rotator cuff tendinitis, elbow disorders, e.g., humeral epicondylitis, and wrist disorders, e.g., tenosynovitis. Between spring 2006 and fall 2008, three occupational health care units in Helsinki referred all eligible patients seeking medical advice for incipient upper extremity pain with symptom duration of less than one month to the Finnish Institute of Occupational Health for further examinations. In the final study population ~~Patients seeking medical advice in the occupational health service due to incipient upper extremity symptoms with symptom duration of less than one month were referred for consultation to the Finnish Institute of Occupational Health from spring 2006 to fall 2008.~~ we included all actively working subjects meeting diagnostic criteria based on physical examination.[16]

We excluded patients whose main problem was a spine or cervical disorder, advanced osteoarthritis, autoimmune disease, fibromyalgia, malignancy, history of recent injury, former surgery related to the current problem, and presence of deformity. We also excluded 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.

Ethics Statement

The Coordinating Ethical Committee of Helsinki University Hospital District has approved this study on 16th of August 2006. All subjects signed an informed consent form before entering the study.

Outcome

Symptoms were determined by the examining physician. A standardized protocol was used that included symptom questions and clinical tests. A v~~V~~isual analogue scale was used to assess pain intensity during the preceding week (0=no pain, 100= highest pain intensity possible). Pain intensity was dichotomized at the highest tertile (cut-point 60).

Independent Variables

We measured body height and weight, and systolic and diastolic blood pressure with standard procedures. Waist circumference was measured halfway between the lowest rib and iliac crest, and hip circumference was measured at the trochanter level. We calculated body mass index (BMI) as body weight in kilograms / (height in meters)^2. The subjects were categorized according to BMI into underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9) and obese (BMI ≥30.0).[17] Waist circumference was grouped into three levels; in men < 94.0 cm, 94.0-101.9 cm, ≥102.0 cm and in women <80.0 cm, 80.0-87.9 cm and ≥88.0 cm.[17] Waist-to-hip ratio was calculated as a ratio of waist circumference and hip circumference and classified into three groups: in men <0.9, 0.9-1.0, >1.0 and in women <0.8, 0.8-0.9 and >0.9.[17 18] Body fat was measured ~~by~~ with the whole body bioimpedance technique (InBody 720, South-Chorea). We

calculated body fat index as total body fat mass in kilograms / (height in meters)^2. In addition, we inquired the use of regular drug treatment.

Fasting blood samples were analysed with Advia 1800® (Siemens Healthcare Diagnostics, USA) for serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and blood glucose as well as serum C-reactive protein (CRP). For lipids we applied clinical cut points recommended by the National Cholesterol Education Program (NCEP) of the National Institutes of Health.[19] We stratified lipid variables in tertiles in case the NCEP cut-points resulted in too small subgroups. Fasting glucose was stratified in tertiles. To identify the metabolic syndrome we used the revised NCEP classification,[20] requiring at least 3 of the following findings: 1) central obesity, defined as waist circumference ≥ 102 cm in men and ≥88 cm in women; 2) high fasting triglycerides, defined as ≥ 1.7 mmol/l (> 150 mg/dL) or drug treatment for elevated triglycerides; 3) low HDL cholesterol defined as < 1.0 mmol/l in men (< 40 mg/dL) and < 1.3 mmol/l (< 50 mg/dL) in women or drug treatment for reduced HDL; 4) elevated blood pressure, defined as 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, defined as fasting glucose ≥ 5.6 mmol/l (100 mg/dL) or drug treatment for elevated glucose.

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High CRP was defined as ≥ 3.0 mg/l.[21] Serum leptin, adiponectin, resistin (DuoSet ELISA R&D systems) and visfatin (Human Visfatin ELISA Kit, AdipoGen) were determined with enzyme-linked immunosorbent assay kits according to the manufacturer's instructions. Adipokines were used as continuous variables and their associations were modeled for one standard deviation increase in their level.

Smoking was classified as never, former, occasional or current. Alcohol consumption was determined as frequency of drinking alcohol per time unit, categorized into none or ≤1

times per month, 2-4 times per month, or ≥2 times per week. Physical exercise was defined as the number of sessions per week of physical activities for at least 30 minutes causing sweating or shortness of breath and categorized into none or sometimes, 1-2, 3-4, or ≥5 times per week.

Exposure to physical load factors was assessed with an interview by a physician. The patients were inquired 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 deviated wrist posture, and the use of vibrating tools. Each factor was dichotomized using a cut-off point of being exposed for ≥10% of the work time during a workday.

We assessed fear-avoidance beliefs with the 4-item Physical Activity subscale of the Fear-Avoidance Beliefs Questionnaire:[22] "physical activity makes my symptoms worse"; "if my symptoms become worse, it means that I should stop what I was doing"; "my pain is caused by work"; and "I should not continue in my present job because of the symptoms". Each item had a 7-point scale from "totally disagree" to "totally agree". We defined fear-avoidance beliefs as high when the score was ≥18 (of maximum of 24).

We evaluated job strain using the "14 item" Job Content Questionnaire (5 for job demands and 9 for job control),[23] each item being assessed with a 5-point scale ranging from "strongly agree" to "strongly disagree". We dichotomized job demand and job control at the median to generate a job strain variable, high demand and low control signifying high job strain.

We used the PHQ-9 questionnaire to assess depressive symptoms.[24] It consists of nine items with a 4-point scale (0 to 3), ranging from 0 to 27. We defined mild to severe depressive symptoms according to the recommended cut-off value of ≥ 5.

Statistical Analysis

We dichotomized pain intensity at the highest tertile. We ran logistic regression models to study the associations of metabolic factors and adipokines with pain intensity controlling for age and gender. Because of small sample size, we first ~~we~~ ran age- and gender-adjusted regression analyses to identify significant covariates within each family of independent variables. We grouped the independent variables into six families and ran six age- and gender-adjusted regression analyses for 1) weight-related factors (BMI, waist circumference and waist-hip ratio); 2) lipids (total cholesterol, LDL-cholesterol, HDL cholesterol, HDL ratio and triglycerides); 3) other metabolic factors (fasting glucose, systolic and diastolic blood pressure and metabolic syndrome); 4) adipokines; 5) other lifestyle factors (smoking, alcohol consumption and physical exercise) and 6) work-related factors (physical load and job strain). ~~Within weight-related factors, lipids, other metabolic factors, adipokines, other lifestyle factors, and work-related factors we ran six additional age and gender adjusted models to identify the factors with a statistically significant association with pain intensity (family-wise analyses).~~ We looked at a possible confounding effect of depressive symptoms with further adjustment in the final models. Stratified analyses were ~~used~~ carried out to assess whether the effects of adipokines

differed between overweight and non-overweight subjects. We used SPSS Statistics 20.0 software for the analysis.

RESULTS

Population characteristics

The subjects were on average 45 years old and predominantly female (Table 1). Fourteen per cent were obese using BMI as an indicator and 10% had high LDL cholesterol (>4.1 mmol/l). Thirty per cent had fasting glucose ≥5.6 mmol/l and 3% ≥7.0 mmol/l. Depressive symptoms were reported by 27% of the patients. Statin treatment was reported by 6% and antihypertensive medication by 15%. None of the patients used fibrate or nicotinic acid treatment. About half (52%) of the patients reported having used painkillers for their upper extremity problem, most of them irregularly. The mean pain intensity was 48. The cut-point for the highest tertile of pain intensity was 60. Subjects with shoulder disorders and epicondylitis each comprised about one third of the study population, and those with non-specific pain one fifth.

Metabolic factors and upper extremity pain

Obesity was associated with pain intensity (Table 2). The association was stronger with waist circumference or waist-to-hip ratio than with BMI. Subjects with low HDL cholesterol, high HDL ratio or high triglyceride levels reported high levels of pain intensity. Those with high job strain reported low pain intensity. The inverse association was partly explained by low waist circumference in those with high job strain (Two-tailed independent samples t-test p=0.007). However, the association between job strain and pain intensity remained statistically significant after further adjustment for waist circumference. Odds ratio of pain intensity for high job strain was 0.3 (0.1-0.9) after adjustment for age, gender and waist circumference.

Fasting glucose, C-reactive protein, blood pressure, metabolic syndrome, leisure time physical exercise, smoking, alcohol consumption, fear avoidance beliefs and physical work load factors showed no associations with pain intensity.

Within weight-related factors waist circumference, within lipids HDL and triglycerides, within adipokines visfatin, and within the group of work-related factors job strain remained statistically significant in the family-wise analyses. In the final models, odds ratio of upper extremity pain was 3.2 (95% CI 1.3-7.9) for abdominal obesity, 4.1 (95% CI 1.5-11.0) for low HDL cholesterol, 3.0 (95% CI 1.2-7.6) for high triglycerides and 1.5 (95% CI 1.0-2.1) for one standard deviation increment of visfatin (Table 3). Further adjustment for depressive symptoms reduced the effects of abdominal obesity and triglycerides on pain intensity.

Waist circumference remained statistically significant with HDL in the model (OR 2.6, 95% CI 1.0-6.9 for abdominal obesity) but not when triglycerides were included in the model (OR 2.4, 95% CI 0.8-6.9). With waist circumference in the final model, OR was 3.2 (95% CI 1.1-9.0) for low HDL cholesterol and 2.3 (95% CI 0.8-6.8) for high triglycerides. ~~The association between visfatin and upper extremity pain was similar in overweight and non-overweight subjects.~~ The association between visfatin and upper extremity pain was similar in overweight and non-overweight subjects. Odds ratio of pain intensity ~~R of~~for visfatin was 1.8 (95% CI 0.6-5.1) among non-overweight subjects ~~1.8 (95% CI 0.6-5.1)~~ and 2.0 (95% CI 0.8-4.6) among overweight/~~ and~~ obese subjects. ~~2.0 (95% CI 0.8-4.6).~~

In a subanalysis including females not on statin or antihypertensive medication and adjusting for age, alcohol consumption and job strain, pain intensity was associated with obesity (OR 2.8, 95% CI 1.0-7.6), HDL cholesterol (OR 4.3, 95% CI 1.5-12.5 for low level), triglycerides (OR 2.6, 95% CI 1.0-7.0 for high level) and visfatin (OR 1.8, 95% CI

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1.1-2.7 for one standard deviation increase in level). With waist circumference in the final model, OR was 3.9 (95% CI 1.3-11.8) for low HDL cholesterol, 2.0 (95 % CI 0.7-6.3) for high triglycerides and 1.6 (95% CI 1.0-2.5) for visfatin.

DISCUSSION

Our study suggests independent associations of abdominal obesity and HDL with upper extremity pain in an inception cohort of patients with non-inflammatory upper extremity disorders. Moreover, of four studied adipokines (leptin, adiponectin, resistin, visfatin) only one (visfatin) was associated with upper extremity pain. Our findings support the role of abdominal obesity in upper extremity pain. Of obesity related indictors we looked at lipids, measures of glucose metabolism, a non-specific marker of inflammation and adipokines, however, our results did not clearly indicate any specific pathomechanical pathway.

We studied three commonly occurring specific soft-tissue disorders of the upper extremity: shoulder disorders (most typically shoulder tendinitis or shoulder impingement syndrome), epicondylitis and tenosynovitis of the wrist. Previous studies have found associations between metabolic factors and these disorders.[9 10] Metabolic factors, such as obesity and lipids have been associated also with carpal tunnel syndrome.[11 12] Moreover, carpal tunnel syndrome may be a result of wrist flexor tenosynovitis.

The associations of weight related factors – especially abdominal obesity measured with waist circumference – point to a possible pain modulating role of abdominal fat in the early stage of UESTDs. Body fat indicators of body-composition did not show an association with upper extremity pain, probably because they do not measure abdominal obesity. The whole body bioimpedance technique is a valid method to estimate body fat percentage in normal or overweight subjects. In obese individuals (BMI ≥30) the accuracy is only moderate.[25] Therefore, waist circumference, as a traditional method of assessing abdominal fat accumulation, can be recommended for studies of UESTDs.

Serum lipids were associated with upper extremity pain, suggesting that they may have an independent role in soft-tissue pain modification at an early stage of UESTDs. We used data-driven cut-points to study the associations of HDL and triglycerides with pain, and the cut-points were lower for triglycerides and higher for HDL cholesterol than the clinical cut-points recommended by NCEP. Only the lowest tertile of HDL cholesterol and the highest tertile of triglycerides were associated with pain intensity.

Adjusting for depressive symptoms decreased slightly the associations of obesity and lipids with pain intensity. Depressive symptoms and obesity are associated and the association seems to be bidirectional.[26] Moreover, depressive symptoms may precede pain or they can be a consequence of pain.[27 28] If depressive symptoms precede pain, not ~~un~~adjusting~~ment~~ for depression will lead to an overestimation of the effects of obesity and lipids on pain. On the other hand, if depressive symptoms are a consequence of pain, adjustment for depression will lead to an underestimation of the effects of obesity and lipids on pain. Depressive people may have a higher perception of pain,[29 30] which would also lead to an overestimation of these associations.

In agreement with our study, some former studies have suggested an association of HDL with musculoskeletal pain.[31] Abdominal obesity, a major feature of the metabolic syndrome, is characteristically associated with systemic low-grade inflammation, as well as with both decreased HDL and increased triglycerides.[12 32] Increased synthesis of e.g. IL-1, a pivotal pro-inflammatory cytokine, may be a mediator in the pathomechanical pathway to increased pain intensity in UESTDs. Moreover, HDL has been shown to be an anti-atherogenic particle and an attenuator of vascular inflammation.[33] Therefore, HDL might also function as a pain modulator owing to its anti-inflammatory properties. Furthermore, increased triglycerides may function as an immunological metabolic stress signal, modifying pain through consecutive pro-inflammatory cascades [34 35]Finally, all

these metabolic factors are involved in the pathomechanism of endothelial dysfunction and subsequent atherosclerosis. [12]

Of the adipokines studied, a high level of circulating visfatin was linked with upper extremity pain. Previous studies of rheumatoid arthritis and osteoarthritis have shown resistin and visfatin expression linking with disease activity,[36 37 38] suggesting indirectly a relationship between adipokines and pain in these conditions. Visfatin is a metabolically active insulin imitator secreted by white adipose tissue and expressed increasingly by fat accumulation. In contrast, in humans other cell types than adipocytes mostly synthesise resistin, such as mononuclear and endothelial cells, unrelated with fat mass. Both resistin and visfatin are pro-inflammatory stimulating for example IL-1 and IL-6 expression that have distinct effects on the musculoskeletal system. In osteoarthritis, for instance, cartilage damage signalling occurs partly by cytokines such as IL-6. In UESTDs, these pro-inflammatory proteins may participate also in pain signalling in cooperation with adipokines. Furthermore, adipokines and lipids may have parallel inflammatory pain signalling pathways in UESTDs.

The population of the current study was predominantly women due to the workplace settings in question such as a central hospital. Due to the small number of men we could not run appropriate regression analyses to see whether the associations found among women were similar in men. Therefore, the findings of this study can be generalized to women only. Moreover, due to cross-sectional nature of the current study causal inference cannot be made.

In conclusion, obesity, especially abdominal obesity and lipids may have an impact on pain intensity in UESTD. They may intensify pain through proinflammatory pain-modifying molecular pathways or by causing soft tissue pathology and dysfunction of their supplying arteries. Of four adipokines studied only one (visfatin) was associated

with pain intensity. In the future, further studies are required to better understand the relationship between metabolic factors and UESTDs.

Contributors

Martti Rechardt was involved in data acquisition, data analysis and interpretation and manuscript drafting. Rahman Shiri was involved in data analysis and interpretation and manuscript drafting. Harri Lindholm was involved in data analysis and interpretation and critically revised the manuscript. Jaro Karppinen was involved in conception and design of the study, data analysis and interpretation and critically revised the manuscript. Eira Viikari-Juntura was in charge of the conception and design of the study, and was involved in data analysis and interpretation and manuscript drafting. All authors approved the final manuscript.

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Competing interests

The authors declare that they have no conflicts of interest.

Patient consent

Each patient gave an informed consent for the study.

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Table 1
Characteristics of the study population (N=163), percentage (%) ~~and 95% confidence interval (CI)~~ or mean (SD).

Characteristic	%	Mean	SD
Age (years)		45.0	9.8
Males	14		
Body mass index (kg/m^2)		25.5	4.3
Waist circumference (cm)		83.4	12.7
Waist-to-hip ratio		0.83	0.08
Fat percent		27.2	8.0
Body fat index (kg/m^2)		6.6	3.9
Total cholesterol (mmol/l)		5.1	0.9
LDL cholesterol (mmol/l)		2.9	0.8
HDL cholesterol (mmol/l)		1.7	0.5
Triglycerides (mmol/l)		1.1	0.6
Fasting glucose (mmol/l)		5.3	0.9
High CRP (≥ 3.0 mg/ml)	18		
Systolic blood pressure (mmHg)		124	17
Diastolic blood pressure (mmHg)		82	11
Adipokines			
Adiponectin (pg/l)		3444	1553
Leptin (pg/l)		14762	12375
Resistin (pg/l)		14662	4481
Visfatin (ng/l)		1.1	0.6
Metabolic syndrome	18		
Current smoking	11		
Alcohol consumption ≥ 2 times per week	19		
Physical exercise ≥ 3 times per week	51		
High physical load	37		
High fear avoidance beliefs score	13		
High job strain	26		
Depressive symptoms	27		
Medication			
Statin	6		
Antihypertensive	15		
Antidiabetic	1		
Antidepressive	4		
Pain intensity (0-100)		48	22
Diagnostic subgroups			
Shoulder disorder	36		
Epicondylitis	31		
Wrist tendinitis or carpal tunnel syndrome	13		
Non-specific pain	20		

Table 2
Age and gender adjusted odd ratios (OR) of pain intensity according to metabolic factors, adipokines, medication, depressive symptoms and work-related factors.

Characteristic	OR	95% CI
Body mass index (kg/m^2)		
<25.0	1	
25.0–29.9	1.9	0.9-4.0
≥30.0	2.1	0.8-5.4
Waist circumference[a]		
Normal	1	
Overweight	1.6	0.6-3.8
Obese	3.2	1.4-7.4
Waist-hip-ratio[b]		
Normal	1	
Overweight	1.0	0.5-2.2
Obese	3.3	1.3-8.6
Fat percent tertile		
<23.3	1	
23.3-30.5	0.9	0.3-2.3
>30.5	1.7	0.7-4.2
Body fat index tertile (kg/m^2)		
<5.13	1	
5.13-7.41	0.9	0.4-2.3
>7.41	1.6	0.7-3.6
Total cholesterol tertile (mmol/l)		
<4.7	1	
4.7-5.3	1.0	0.4-2.7
>5.3	1.8	0.8-4.0
LDL cholesterol tertile (mmol/l)		
<2.5	1	
2.5-3.3	1.1	0.4-2.6
>3.3	1.7	0.7-4.2
HDL cholesterol tertile (mmol/l)		
>1.83	1	
1..48-1.83	0.9	0.4-2.2
<1.48	2.7	1.2-6.3
HDL ratio tertile		
<2.73	1	
2.73–3.31	2.8	1.2-6.9
>3.31	2.6	1.1-6.4
Triglycerides tertile (mmol/l)		
<0.72	1	
0.72–1.08	1.7	0.7-4.0
>1.08	2.8	1.2-6.6
Adipokines[c]		
Adiponectin	0.9	0.6-1.3
Leptin	1.2	0.9-1.8
Resistin	1.2	0.8-1.6
Visfatin	1.4	1.0-2.0
Medication		
Statin	0.9	0.2-4.3
Antihypertensive	1.5	0.6-3.8
Antidepressive	1.2	0.2-7.6
Depressive symptoms	2.5	1.2-5.2
Physical load	1.5	0.7-3.1
Job Strain	0.2	0.1-0.7
Fear avoidance beliefs	1.2	0.4-3.4

[a] Normal: Men <94 cm, Women <80 cm; Overweight Men 94-101.9 cm, Women 80-87.9 cm; Obese Men ≥102 cm, Women ≥88 cm.
[b] Normal: Men <0.9, Women <0.8; Overweight: Men 0.9-1.0; Obese: Women 0.8-0.9 Men >1.0; Women >0.9.
[c] Continuous variable; increment of one SD

Table 3
The associations of obesity, lipids and adipokines with upper extremity pain intensity

	OR[c]	95% CI	OR[d]	95% CI
Waist circumference [a]				
Normal	1		1	
Overweight	1.2	0.5-3.2	1.2	0.4-3.2
Obese	3.2	1.3-7.9	2.9	1.1-7.3
HDL cholesterol tertile (mmol/l)				
>1.83	1		1	
1.48–1.83	0.8	0.3-2.2	0.7	0.2-2.0
<1.48	4.1	1.5-11.0	3.9	1.4-10.1
Triglycerides tertile (mmol/l)				
<0.72	1		1	
0.72–1.08	1.6	0.6-4.1	1.4	0.5-3.8
>1.08	3.0	1.2-7.6	2.6	1.0-6.8
Visfatin[b]	1.5	1.0-2.1	1.4	1.0-2.1

[a] Normal: Men <94 cm, Women <80 cm; Overweight: Men 94-101.9 cm , Women 80-87.9 cm; Obese: Men ≥102 cm, Women ≥88 cm.
[b] Continuous variable; increment of one SD
[c] Adjusted for age, gender, statin medication, alcohol consumption and job strain.
[d] Further adjustment for depressive symptoms

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The associations of metabolic factors and adipokines with pain in incipient upper extremity soft tissue disorders: a cross-sectional study

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ABSTRACT

Objectives: Earlier studies have suggested associations between metabolic factors and musculoskeletal pain or disorders. We studied the associations of obesity, lipids, other features of the metabolic syndrome and adipokines (adiponectin, leptin, resistin, visfatin) with upper extremity pain in a clinical population with incipient UESTDs.

Design: A cross-sectional study.

Setting: Primary health care (occupational health service) with further examinations at a research institute.

Participants: Patients (N=163) seeking medical advice in the occupational health service due to incipient upper extremity symptoms with symptom duration of less than one month were referred for consultation to the Finnish Institute of Occupational Health from spring 2006 to fall 2008. We included all actively working subjects meeting diagnostic criteria based on physical examination. We excluded subjects meeting predetermined conditions.

Outcome measure: Pain intensity was assessed with visual analogue scale and dichotomized at the highest tertile (cut-point 60).

Results: Obesity (adjusted odds ratio (OR) for high waist circumference 2.9, 95% CI 1.1-7.3), HDL cholesterol (OR 3.9, 95% CI 1.4-10.1 for low level) and triglycerides (OR 2.6, 95% CI 1.0-6.8 for high level) were associated with pain intensity. Of four adipokines studied, only visfatin was associated with upper extremity pain (adjusted OR 1.4, 95% CI 1.0-2.1 for one standard deviation increase in level).

Conclusions: Abdominal obesity and lipids may have an impact on pain intensity in UESTDs. They may intensify pain through proinflammatory pain-modifying molecular pathways or by causing soft tissue pathology and dysfunction of their supplying arteries. Of four adipokines studied only one (visfatin) was associated with pain intensity. In the future, further studies are required to better understand the relationship between metabolic factors and UESTDs.

ARTICLE SUMMARY

Article focus:

- We studied the associations of metabolic factors, serum C-reactive protein and adipokines with upper extremity pain intensity among subjects with incipient upper extremity soft tissue disorders (UESTDs).

Key messages:

- Subjects with abdominal obesity, low levels of high-density lipoprotein (HDL) cholesterol, or high levels of the adipokine visfatin reported higher upper extremity pain intensity than those with normal waist circumference, higher levels of HDL cholesterol, or low levels of visfatin.
- Further studies are needed to understand the role of metabolic factors in UESTDs.

Strengths and limitations of the study:

- Strengths of the study include: 1) Metabolic factors and adipokines were measured, and 2) Patients with early stage of upper extremity soft tissue disorders were included in the study.
- Limitations of the study include: 1) Small sample size, 2) Cross sectional design of the study.

INTRODUCTION

Upper extremity pain is a common health problem in general populations. The prevalence of forearm pain during the preceding 30 days has been estimated at 8%, [1] and that of shoulder pain has ranged between 12% and 30%.[1-4] In the general population, one of five persons reports chronic upper extremity pain.[5] Common causes for upper extremity pain include soft tissue disorders, such as rotator cuff tendinitis, epicondylitis and tenosynovitis.[6]

Some studies have suggested an association between musculoskeletal pain or disorders and metabolic factors, such as obesity, lipids and hyperglycaemia.[7-9] In a French working population study, obese men and diabetic women had a significantly higher occurrence of upper extremity soft tissue disorders (UESTDs) compared to subjects without such metabolic disorders.[10] In addition, an association has been reported between carpal tunnel syndrome and serum lipids.[11 12]

Obesity is often an underlying factor for dyslipidemia and disturbances of glucose metabolism. It may cause a systemic low grade inflammation and increased pro-inflammatory activity with elevated cytokine levels.[13] Dyslipidemia may cause accumulation of lipids on musculoskeletal structures, e.g., tendons.[14 15] Advanced glycation end-products may accumulate in hyperglycaemia resulting in latent collagen and microvascular alterations.[16 17]

Adipokines are proteins largely released by adipocytes, typically showing increased production in obesity. Characteristically, they exert widespread effects on immunological processes for example by stimulating cytokine expression. Adipokines function also in musculoskeletal disorders, best documented in degenerative inflammatory joint

conditions.[18] We are not aware of studies on the role of adipokines in non-inflammatory upper extremity disorders.

We studied the associations of obesity, lipids, other features of the metabolic syndrome and adipokines with upper extremity pain in a clinical population with incipient UESTDs. We hypothesised that UESTD patients with obesity, dyslipidemia, high C-reactive protein and adipokines report higher levels of pain intensity than patients without these risk factors. Furthermore, we explored whether the associations of adipokines with upper extremity pain differ in overweight and non-overweight subjects.

METHODS

Patients

This cross-sectional study was a part of a larger project on metabolic and inflammatory factors in UESTDs. Included conditions were shoulder disorders, e.g., rotator cuff tendinitis, elbow disorders, e.g., humeral epicondylitis, and wrist disorders, e.g., tenosynovitis. Patients seeking medical advice in the occupational health service due to incipient upper extremity symptoms with symptom duration of less than one month were referred for consultation to the Finnish Institute of Occupational Health from spring 2006 to fall 2008. We included all actively working subjects meeting diagnostic criteria based on physical examination.[19]

We excluded patients whose main problem was a spine or cervical disorder, advanced osteoarthritis, autoimmune disease, fibromyalgia, malignancy, history of recent injury, former surgery related to the current problem, and presence of deformity. We also excluded 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.

Ethics Statement

The Coordinating Ethical Committee of Helsinki University Hospital District has approved this study on 16th of August 2006. All subjects signed an informed consent form before entering the study.

Outcome

Symptoms were determined by the examining physician. A standardized protocol was used that included symptom questions and clinical tests. Visual analogue scale was used to assess pain intensity during the preceding week (0=no pain, 100= highest pain intensity possible). Pain intensity was dichotomized at the highest tertile (cut-point 60).

Independent Variables

We measured body height and weight, and systolic and diastolic blood pressure with standard procedures. Waist circumference was measured halfway between the lowest rib and iliac crest, and hip circumference was measured at the trochanter level. We calculated body mass index (BMI) as body weight in kilograms / (height in meters)^2. The subjects were categorized according to BMI into underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9) and obese (BMI $\geq$30.0).[20] Waist circumference was grouped into three levels; in men < 94.0 cm, 94.0-101.9 cm, $\geq$102.0 cm and in women <80.0 cm, 80.0-87.9 cm and $\geq$88.0 cm.[20] Waist-to-hip ratio was calculated as a ratio of waist circumference and hip circumference and classified into three groups: in men <0.9, 0.9-1.0, >1.0 and in women <0.8, 0.8-0.9 and >0.9.[20 21] Body fat was measured by the whole body bioimpedance technique (InBody 720, South-Chorea). We calculated body fat index as total body fat mass in kilograms / (height in meters)^2. In addition, we inquired the use of regular drug treatment.

Fasting blood samples were analysed with Advia 1800® (Siemens Healthcare Diagnostics, USA) for serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density

lipoprotein (LDL) cholesterol, triglycerides and blood glucose as well as serum C-reactive protein (CRP). For lipids we applied clinical cut points recommended by the National Cholesterol Education Program (NCEP) of the National Institutes of Health.[22] We stratified lipid variables in tertiles in case the NCEP cut-points resulted in too small subgroups. Fasting glucose was stratified in tertiles. To identify the metabolic syndrome we used the revised NCEP classification,[23] requiring at least 3 of the following findings: 1) central obesity, defined as waist circumference ≥ 102 cm in men and ≥88 cm in women; 2) high fasting triglycerides, defined as ≥ 1.7 mmol/l (> 150 mg/dL) or drug treatment for elevated triglycerides; 3) low HDL cholesterol defined as < 1.0 mmol/l in men (< 40 mg/dL) and < 1.3 mmol/l (< 50 mg/dL) in women or drug treatment for reduced HDL; 4) elevated blood pressure, defined as 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, defined as fasting glucose ≥ 5.6 mmol/l (100 mg/dL) or drug treatment for elevated glucose.

High CRP was defined as ≥ 3.0 mg/l.[24] Serum leptin, adiponectin, resistin (DuoSet ELISA R&D systems) and visfatin (Human Visfatin ELISA Kit, AdipoGen) were determined with enzyme-linked immunosorbent assay kits according to the manufacturer's instructions. Adipokines were used as continuous variables and their associations were modeled for one standard deviation increase in their level.

Smoking was classified as never, former, occasional or current. Alcohol consumption was determined as frequency of drinking alcohol per time unit, categorized into none or ≤1 times per month, 2-4 times per month, or ≥2 times per week. Physical exercise was defined as the number of sessions per week of physical activities for at least 30 minutes

causing sweating or shortness of breath and categorized into none or sometimes, 1-2, 3-4, or ≥5 times per week.

Exposure to physical load factors was assessed with an interview by a physician. The patients were inquired 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 deviated wrist posture, and the use of vibrating tools. Each factor was dichotomized using a cut-off point of being exposed for ≥10% of the work time during a workday.

We assessed fear-avoidance beliefs with the 4-item Physical Activity subscale of the Fear-Avoidance Beliefs Questionnaire:[25] "physical activity makes my symptoms worse"; "if my symptoms become worse, it means that I should stop what I was doing"; "my pain is caused by work"; and "I should not continue in my present job because of the symptoms". Each item had a 7-point scale from "totally disagree" to "totally agree". We defined fear-avoidance beliefs as high when the score was ≥18 (of maximum of 24).

We evaluated job strain using the "14 item" Job Content Questionnaire (5 for job demands and 9 for job control),[26] each item being assessed with a 5-point scale ranging from "strongly agree" to "strongly disagree". We dichotomized job demand and job control at the median to generate a job strain variable, high demand and low control signifying high job strain.

We used the PHQ-9 questionnaire to assess depressive symptoms.[27] It consists of nine items with a 4-point scale (0 to 3), ranging from 0 to 27. We defined mild to severe depressive symptoms according to the recommended cut-off value of ≥ 5.

Statistical Analysis

We dichotomized pain intensity at the highest tertile. We ran logistic regression models to study the associations of metabolic factors and adipokines with pain intensity controlling for age and gender. Within weight-related factors, lipids, other metabolic factors, adipokines, other lifestyle factors, and work-related factors we ran six additional age and gender adjusted models to identify the factors with a statistically significant association with pain intensity (family-wise analyses). We looked at a possible confounding effect of depressive symptoms with further adjustment in the final models. Stratified analyses were used to assess whether the effects of adipokines differed between overweight and non-overweight subjects. We used SPSS Statistics 20.0 software for the analysis.

RESULTS

Population characteristics

The subjects were on average 45 years old and predominantly female (Table 1). Fourteen per cent were obese using BMI as an indicator and 10% had high LDL cholesterol (>4.1 mmol/l). Thirty per cent had fasting glucose ≥5.6 mmol/l and 3% ≥7.0 mmol/l. Depressive symptoms were reported by 27% of the patients. Statin treatment was reported by 6% and antihypertensive medication by 15%. None of the patients used fibrate or nicotinic acid treatment. About half (52%) of the patients reported having used painkillers for their upper extremity problem, most of them irregularly. The mean pain intensity was 48. The cut-point for the highest tertile of pain intensity was 60. Subjects with shoulder disorders and epicondylitis each comprised about one third of the study population, and those with non-specific pain one fifth.

Metabolic factors and upper extremity pain

Obesity was associated with pain intensity (Table 2). The association was stronger with waist circumference or waist-to-hip ratio than with BMI. Subjects with low HDL cholesterol, high HDL ratio or high triglyceride levels reported high levels of pain intensity. Those with high job strain reported low pain intensity. The inverse association was partly explained by low waist circumference in those with high job strain (Two-tailed independent samples t-test p=0.007).

Fasting glucose, C-reactive protein, blood pressure, metabolic syndrome, leisure time physical exercise, smoking, alcohol consumption, fear avoidance beliefs and physical work load factors showed no associations with pain intensity.

Within weight-related factors waist circumference, within lipids HDL and triglycerides, within adipokines visfatin, and within the group of work-related factors job strain remained statistically significant in the family-wise analyses. In the final models, odds ratio of upper extremity pain was 3.2 (95% CI 1.3-7.9) for abdominal obesity, 4.1 (95% CI 1.5-11.0) for low HDL cholesterol, 3.0 (95% CI 1.2-7.6) for high triglycerides and 1.5 (95% CI 1.0-2.1) for one standard deviation increment of visfatin (Table 3). Further adjustment for depressive symptoms reduced the effects of abdominal obesity and triglycerides on pain intensity.

Waist circumference remained statistically significant with HDL in the model (OR 2.6, 95% CI 1.0-6.9 for abdominal obesity) but not when triglycerides were included in the model (OR 2.4, 95% CI 0.8-6.9). With waist circumference in the final model, OR was 3.2 (95% CI 1.1-9.0) for low HDL cholesterol and 2.3 (95% CI 0.8-6.8) for high triglycerides. The association between visfatin and upper extremity pain was similar in overweight and non-overweight subjects.

In a subanalysis including females and those not on statin or antihypertensive medication and adjusting for age, alcohol consumption and job strain, pain intensity was associated with obesity (OR 2.8, 95% CI 1.0-7.6), HDL cholesterol (OR 4.3, 95% CI 1.5-12.5 for low level), triglycerides (OR 2.6, 95% CI 1.0-7.0 for high level) and visfatin (OR 1.8, 95% CI 1.1-2.7 for one standard deviation increase in level). With waist circumference in

the final model, OR was 3.9 (95% CI 1.3-11.8) for low HDL cholesterol, 2.0 (95 % CI 0.7-6.3) for high triglycerides and 1.6 (95% CI 1.0-2.5) for visfatin.

DISCUSSION

Our study suggests independent associations of abdominal obesity and HDL with upper extremity pain in an inception cohort of patients with non-inflammatory upper extremity disorders. Moreover, of four studied adipokines (leptin, adiponectin, resistin, visfatin) only one (visfatin) was associated with upper extremity pain. Our findings support the role of abdominal obesity in upper extremity pain. Of obesity related indictors we looked at lipids, measures of glucose metabolism, a non-specific marker of inflammation and adipokines, however, our results did not clearly indicate any specific pathomechanical pathway.

The associations of weight related factors – especially abdominal obesity measured with waist circumference – point to a possible pain modulating role of abdominal fat in the early stage of UESTDs. Body fat indicators of body-composition did not show an association with upper extremity pain, probably because they do not measure abdominal obesity. The whole body bioimpedance technique is a valid method to estimate body fat percentage in normal or overweight subjects. In obese individuals (BMI ≥30) the accuracy is only moderate.[28] Therefore, waist circumference, as a traditional method of assessing abdominal fat accumulation, can be recommended for studies of UESTDs.

Serum lipids were associated with upper extremity pain, suggesting that they may have an independent role in soft-tissue pain modification at an early stage of UESTDs. We used data-driven cut-points to study the associations of HDL and triglycerides with pain, and the cut-points were lower for triglycerides and higher for HDL cholesterol than the clinical cut-points recommended by NCEP. Accordingly, our study showed associations

between lipids and upper extremity pain at lipid levels not considered to increase cardiovascular disease risk.

Adjusting for depressive symptoms decreased slightly the associations of obesity and lipids with pain intensity. Depressive symptoms and obesity are associated and the association seems to be bidirectional.[29] Moreover, depressive symptoms may precede pain or they can be a consequence of pain.[30 31] If depressive symptoms precede pain, unadjustment for depression will lead to an overestimation of the effects of obesity and lipids on pain. On the other hand, if depressive symptoms are a consequence of pain, adjustment for depression will lead to an underestimation of the effects of obesity and lipids on pain. Depressive people may have a higher perception of pain,[32 33] which would also lead to an overestimation of these associations.

In agreement with our study, some former studies have suggested an association of HDL with musculoskeletal pain.[34] Abdominal obesity, a major feature of the metabolic syndrome, is characteristically associated with systemic low-grade inflammation, as well as with both decreased HDL and increased triglycerides.[15 35] Increased synthesis of e.g. IL-1, a pivotal pro-inflammatory cytokine, may be a mediator in the pathomechanical pathway to increased pain intensity in UESTDs. Moreover, HDL has been shown to be an anti-atherogenic particle and an attenuator of vascular inflammation.[36] Therefore, HDL might also function as a pain modulator owing to its anti-inflammatory properties. Furthermore, increased triglycerides may function as an immunological metabolic stress signal, modifying pain through consecutive pro-inflammatory cascades [13 37]Finally, all these metabolic factors are involved in the pathomechanism of endothelial dysfunction and subsequent atherosclerosis. [15]

Of the adipokines studied, a high level of circulating visfatin was linked with upper extremity pain. Previous studies of rheumatoid arthritis and osteoarthritis have shown resistin and visfatin expression linking with disease activity,[38 39 40] suggesting indirectly a relationship between adipokines and pain in these conditions. Visfatin is a metabolically active insulin imitator secreted by white adipose tissue and expressed increasingly by fat accumulation. In contrast, in humans other cell types than adipocytes mostly synthesise resistin, such as mononuclear and endothelial cells, unrelated with fat mass. Both resistin and visfatin are pro-inflammatory stimulating for example IL-1 and IL-6 expression that have distinct effects on the musculoskeletal system. In osteoarthritis, for instance, cartilage damage signalling occurs partly by cytokines such as IL-6. In UESTDs, these pro-inflammatory proteins may participate also in pain signalling in cooperation with adipokines. Furthermore, adipokines and lipids may have parallel inflammatory pain signalling pathways in UESTDs.

In conclusion, obesity, especially abdominal obesity and lipids may have an impact on pain intensity in UESTD. They may intensify pain through proinflammatory pain-modifying molecular pathways or by causing soft tissue pathology and dysfunction of their supplying arteries. Of four adipokines studied only one (visfatin) was associated with pain intensity. In the future, further studies are required to better understand the relationship between metabolic factors and UESTDs.

Contributors

Martti Rechardt was involved in data acquisition, data analysis and interpretation and manuscript drafting. Rahman Shiri was involved in data analysis and interpretation and manuscript drafting. Harri Lindholm was involved in data analysis and interpretation and critically revised the manuscript. Jaro Karppinen was involved in conception and design of the study, data analysis and interpretation and critically revised the manuscript. Eira Viikari-Juntura was in charge of the conception and design of the study, and was involved in data analysis and interpretation and manuscript drafting. All authors approved the final manuscript.

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Competing interests

The authors declare that they have no conflicts of interest.

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Table 1
Characteristics of the study population (N=163), percentage (%) and 95% confidence interval (CI) or mean (SD).

Characteristic	%	95% CI	Mean	SD
Age (years)			45.0	9.8
Males	14			
Body mass index (kg/m^2)			25.5	4.3
Waist circumference (cm)			83.4	12.7
Waist-to-hip ratio			0.83	0.08
Fat percent			27.2	8.0
Body fat index (kg/m^2)			6.6	3.9
Total cholesterol (mmol/l)			5.1	0.9
LDL cholesterol (mmol/l)			2.9	0.8
HDL cholesterol (mmol/l)			1.7	0.5
Triglycerides (mmol/l)			1.1	0.6
Fasting glucose (mmol/l)			5.3	0.9
High CRP (≥ 3.0 mg/ml)	18	12-24		
Systolic blood pressure (mmHg)			124	17
Diastolic blood pressure (mmHg)			82	11
Adipokines				
Adiponectin (pg/l)			3444	1553
Leptin (pg/l)			14762	12375
Resistin (pg/l)			14662	4481
Visfatin (ng/l)			1.1	0.6
Metabolic syndrome	18	12-24		
Current smoking	11	6-16		
Alcohol consumption ≥ 2 times per week	19	13-25		
Physical exercise ≥ 3 times per week	51	43-59		
High physical load	37	30-45		
High fear avoidance beliefs score	13	7-18		
High job strain	26	19-33		
Depressive symptoms	27	20-33		
Medication				
Statin	6	2-9		
Antihypertensive	15	9-20		
Antidiabetic	1	0-3		
Antidepressive	4	1-7		
Pain intensity (0-100)			48	22
Diagnostic subgroups				
Shoulder disorder	36	28-43		
Epicondylitis	31	24-38		
Wrist tendinitis or carpal tunnel syndrome	13	8-18		
Non-specific pain	20	14-26		

Table 2
Age and gender adjusted odd ratios (OR) of pain intensity according to metabolic factors, adipokines, medication, depressive symptoms and work-related factors.

Characteristic	OR	95% CI
Body mass index (kg/m^2)		
<25.0	1	
25.0–29.9	1.9	0.9-4.0
≥30.0	2.1	0.8-5.4
Waist circumference[a]		
Normal	1	
Overweight	1.6	0.6-3.8
Obese	3.2	1.4-7.4
Waist-hip-ratio[b]		
Normal	1	
Overweight	1.0	0.5-2.2
Obese	3.3	1.3-8.6
Fat percent tertile		
<23.3	1	
23.3-30.5	0.9	0.3-2.3
>30.5	1.7	0.7-4.2
Body fat index tertile (kg/m^2)		
<5.13	1	
5.13-7.41	0.9	0.4-2.3
>7.41	1.6	0.7-3.6
Total cholesterol tertile (mmol/l)		
<4.7	1	
4.7-5.3	1.0	0.4-2.7
>5.3	1.8	0.8-4.0
LDL cholesterol tertile (mmol/l)		
<2.5	1	
2.5-3.3	1.1	0.4-2.6
>3.3	1.7	0.7-4.2
HDL cholesterol tertile (mmol/l)		
>1.83	1	
1..48-1.83	0.9	0.4-2.2
<1.48	2.7	1.2-6.3
HDL ratio tertile		
<2.73	1	
2.73–3.31	2.8	1.2-6.9
>3.31	2.6	1.1-6.4
Triglycerides tertile (mmol/l)		
<0.72	1	
0.72–1.08	1.7	0.7-4.0
>1.08	2.8	1.2-6.6
Adipokines[c]		
Adiponectin	0.9	0.6-1.3
Leptin	1.2	0.9-1.8
Resistin	1.2	0.8-1.6
Visfatin	1.4	1.0-2.0
Medication		
Statin	0.9	0.2-4.3
Antihypertensive	1.5	0.6-3.8
Antidepressive	1.2	0.2-7.6
Depressive symptoms	2.5	1.2-5.2
Physical load	1.5	0.7-3.1
Job Strain	0.2	0.1-0.7
Fear avoidance beliefs	1.2	0.4-3.4

[a] Normal: Men <94 cm, Women <80 cm; Overweight Men 94-101.9 cm, Women 80-87.9 cm; Obese Men ≥102 cm, Women ≥88 cm.
[b] Normal: Men <0.9, Women <0.8; Overweight: Men 0.9-1.0; Obese: Women 0.8-0.9 Men >1.0; Women >0.9.
[c] Continuous variable; increment of one SD

Table 3
The associations of obesity, lipids and adipokines with upper extremity pain intensity

	OR[c]	95% CI	OR[d]	95% CI
Waist circumference [a]				
Normal	1		1	
Overweight	1.2	0.5-3.2	1.2	0.4-3.2
Obese	3.2	1.3-7.9	2.9	1.1-7.3
HDL cholesterol tertile (mmol/l)				
>1.83	1		1	
1.48–1.83	0.8	0.3-2.2	0.7	0.2-2.0
<1.48	4.1	1.5-11.0	3.9	1.4-10.1
Triglycerides tertile (mmol/l)				
<0.72	1		1	
0.72–1.08	1.6	0.6-4.1	1.4	0.5-3.8
>1.08	3.0	1.2-7.6	2.6	1.0-6.8
Visfatin[b]	1.5	1.0-2.1	1.4	1.0-2.1

[a] Normal: Men <94 cm, Women <80 cm; Overweight: Men 94-101.9 cm , Women 80-87.9 cm; Obese: Men ≥102 cm, Women ≥88 cm.
[b] Continuous variable; increment of one SD
[c] Adjusted for age, gender, statin medication, alcohol consumption and job strain.
[d] Further adjustment for depressive symptoms