

Correlation between cardiovascular co-morbidity, inflammation and
pain in patients with rheumatoid arthritis, an observational study

Master thesis in Medicine

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Abstract

Background Rheumatoid arthritis (RA) is a chronic autoimmune disease, characterized by persistent inflammation and damage of joints. About 1% of the Swedish population is diagnosed with RA, and it is three times more common in women than in men.

Purpose The aim of this study was to analyse a link between pain, inflammation and cardiovascular comorbidity in a cohort of patients with established RA.

Method Data collected from 198 patients (women and men) diagnosed with RA were analysed regarding the history of cardiovascular (CV) events and current CV medications, pain perception and disease activity. Disease activity score, visual analogue scale, tender points, blood lipid profile, smoking habits, body mass index were taken into account.

Results In the study cohort, 19% of women and 50% of men reported to have CV co-morbidity, indicating that women had four times lower self-reported CV co-morbidity (OR 0.23, [CI 95% 0.11-0.49]). Women had significantly lower BMI* and triglycerides* as well as higher HDL* than men. It was discovered that men without CVC and men with CVC were similar when comparing risk factors for developing CVC. On the other hand, women with CVC and women without CVC had significant differences in BMI*, triglycerides* and age*. Women experienced more pain than men did when valued tender points as they had a significant higher number of tender points than men*.

Conclusions Fewer women than men had cardiovascular co-morbidity. Women with CVC do follow traditional pattern of risk factors for CVC whereas men without CVC and men with CVC were similar when comparing risk factors for developing CVC. Women and men perceive pain differently when value tender points. CVC do not tend to contribute to an increased pain in women or in men.

Key words Rheumatoid arthritis, cardiovascular co-morbidity

(*p<0.05)

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent systemic and local inflammation in the joints, which includes synovial inflammation and hyperplasia, and damage of cartilage and periarticular bone destruction. Production of autoantibodies is an early biological marker of the disease, which may be present several years ahead of clinical symptoms of the joint inflammation. RA is associated with cardiovascular, pulmonary and skeletal disorders. The mortality rate among patients with RA is higher than among the general population of the same age.⁽¹⁾

About 1% of the population is diagnosed with RA and it is three times more common in women than in men.^(2, 3) The factors predisposing to the development of RA consist of a combination of genetic and environmental factors in their coincidence. An example of a genetic factor, is the association with the human leukocyte antigen (HLA) –DRB1 locus which has been noticed in RA patients who are positive for rheumatoid factor, RF or anti-citrullinated protein antibody, ACPA. Environmental factors include smoking, dust exposure and infectious agents such as Epstein-Barr virus, cytomegalovirus and *Escherichia coli*. They have been associated with RA, probably due to the development of autoantibodies caused by these infectious agents. For some people, the risk of developing RA is increased by smoking.⁽¹⁾

Patient`s who is considered to have Rheumatoid arthritis but are in absence of positive rheumatoid factor, have seronegative Rheumatoid arthritis. The development of seronegative RA is probably due to hormonal factors. Early menopause in women and low testosterone levels in women and men has been associated with seronegative RA. Moreover, hormonal changes are believed to influence pathogenesis and disease progression. During the peri- and postmenopausal period in women, high incidence of RA is found.^(4, 5)

Cardiovascular (CV) morbidity and mortality in RA patients is high and comparable to patients with diabetes mellitus.⁽⁶⁻⁸⁾ Recent studies showed that patients with RA often die of CV disease, resulting in decreased life expectancy.⁽⁸⁻¹⁰⁾ It has been observed that RA is associated with a 50-60% increased risk of CV death.^(6, 9) It has also been shown that patients with RA have a double risk of ischemic heart disease, and that CV risk factors are seen more frequently in RA patients.^(6, 8, 11)

The high risk for cardiovascular diseases is namely mostly due to the inflammatory burden in RA.⁽¹²⁾ The association between Rheumatoid arthritis and increased rates of cardiovascular illness is explained partly by inflammatory mediators. Cytokines and acute-phase reactants increase endothelial activation and potentially render atheromatous plaques unstable. Moreover, cytokines themselves affect muscle and adipose tissues in making them insulin-resistant.⁽¹⁾

The typical and well-established CV risk factors include dyslipidaemia, diabetes mellitus, hypertension and higher body mass index (BMI).⁽⁷⁾ On the other hand, it has also been reported that other risk factors such as smoking, lipid patterns and male gender have less influence in RA patients for developing CV co-morbidity.⁽¹³⁾ There are also differences between women and men regarding development of cardiovascular morbidity. Men in general have a higher risk of developing CVC many years earlier than women.⁽¹⁴⁾ Furthermore, a prospective observational study performed in Gothenburg, Sweden on 1462 randomly selected women aged 30-60, showed that triglycerides are one of the most important values when calculating risk factors for both total mortality and death from myocardial infarction, in women.⁽¹⁵⁾

The complexity of valuing traditional risk factors in RA patients is demonstrated when value cholesterol and low-density lipoprotein (LDL). They have been shown to have a paradoxical impact on risk for CV co-morbidity since they tend to decrease on the onset of RA.⁽¹³⁾ Even

tough high BMI is associated with the increased risk for CV co-morbidity in the general population; studies have shown that RA patients with BMI above 30 had lower mortality in CV disease than RA patients with lower BMI.^(16, 17) On the other hand, increasing BMI and obesity leads to difficulties to reach disease remission in RA. Obesity is also associated with worse RA outcome and co-morbidities such as hypertension.⁽¹⁸⁾ In summary, dyslipidaemia, hypertension, diabetes mellitus and decreased physical activity, all associated with CV co-morbidity, occur more frequently in RA patients. As RA itself imply an inflammatory process and in combination with above stated risk factors for developing CVC, patients could have an increased risk of CV co-morbidity.⁽⁸⁾

Increased risk of CV co-morbidity could be related to RA treatment. An early start of anti-rheumatic treatment is associated with reduced CV risk.⁽⁸⁾ The majority of RA patients are long-term users of the non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying drugs. It is shown that NSAIDs as well as corticosteroids are associated with increased risk of CV disease.⁽⁸⁾ On the other hand, disease-modifying drugs such as methotrexate and biological drugs could reduce the risk of CV events including myocardial infarction.^(6, 9) However, research regarding biological needs further randomised controlled trials to support findings within this field as well as to improve treatment of patients with these drugs.⁽¹⁹⁾

RA patients describe pain as one of the most worrying difficulties in coping with their disease.⁽¹⁶⁾ Pain affects patient's sleep, leads to psychological distress as well as impact on disability. It's believed that pain arises from joint inflammation, structural joint damage and central sensitization.⁽²⁰⁾ Physical disability in patients with RA leads to decreased quality of

life.⁽²¹⁾ Less is known about severe pain in RA but high disease activity is associated with RA pain.⁽²⁰⁾

Furthermore, pain perception is complex, including both sensory and psychological parts. Pollard et al. have demonstrated this by setting up an observational study where they measured pain thresholds using an algometer. Their results showed that pain thresholds correlated with disease activity (tender joint counts), fatigue, anxiety and depression. Furthermore, RA patients with over eleven tender points have lower pain threshold. This is also true for patients with disease duration over ten years.⁽²²⁾ Moreover, to describe the complexity of perception of pain, studies have shown that men and women perceive pain differently. Women are more sensitive when graduating tender points than men are.^(23, 24)

Deeper knowledge about mechanisms of pain in RA would be of great importance for patients. Since the increased risk of CV events is not completely understood and the mechanism is complex, this study investigates a potential link between CV co-morbidity, pain and inflammation in RA patients visiting the Sahlgrenska University Hospital and being treated with methotrexate. A correlation between self-rated pain perception, tender points, and inflammation markers has been noticed.⁽²⁵⁾ We had a hypothesis that there could be a correlation between CV co-morbidity, perception of pain and inflammation markers. The aim of this study was to analyse a link between pain, inflammation and cardiovascular comorbidity in a cohort of patients with established RA.

Material and Methods

Patients

Data were collected from patients who fulfilled the classification criteria of RA proposed by American College of Rheumatology (ACR) 1987. According to ACR 1987, for diagnose rheumatoid arthritis; a patient should satisfy at least 4 of 7 criteria. The criteria including; morning stiffness, arthritis of 3 or more joint areas, arthritis of hand joints, symmetric arthritis, rheumatoid nodules, serum rheumatoid factor and radiographic changes.⁽²⁶⁾ All patients with the diagnosis of RA, treated with methotrexate (MTX) and regularly patients at the Rheumatology Clinics Sahlgrenska University Hospital were eligible for the study. In total, 626 patients were retrieved from the list of MTX-users at the Rheumatology Clinics and were invited to participate in the study. One hundred ninety eight (198) patients participated unconstrained in the study and underwent a physical examination and filled in the self-assessment questionnaire. Of them, 174 patients (132 females and 42 males) were included in the analysis and 24 patients were excluded from further analysis due to lack of complete information about their current medication.

In this study, patients from Sahlgrenska University Methotrexate register were used. The argument for using patients treated with methotrexate is because patients who receive methotrexate have severe RA. Methotrexate is the most commonly used RA treatment and is used for patient in need of sufficient treatment. It was also an opportunity to compare patients who receive comparable treatment.

Clinical assessment and Laboratory parameters

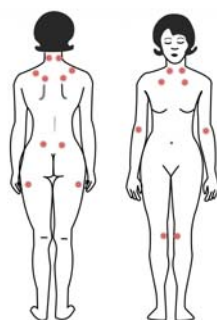
The CV co-morbidity was defined by patient's anamnesis of CV event and/or by the use of medical treatment as statins, acetylsalicylic acid/warfarin or hypotensives. The patient cohort

was stratified by gender and by CV co-morbidity. The analysis was performed with respect to general CV risk factors: BMI, age, smoking habits, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides levels. BMI was calculated as weight (kg)/length (m)².

To value RA inflammation, disease activity score, DAS28 was assessed. DAS28 is a commonly used instrument based on a cumulative index composed of erythrocyte sedimentation rate (ESR) (or c-reactive protein (CRP)), global patients self-assessment of health and number of swollen and tender joints.^(2, 20, 27, 28) All patients are divided into the three commonly used groups depending on their individual DAS28 score.⁽²⁹⁾ The three groups are: *Remission* (DAS28<3.2), *Active* (DAS28 3.2 - <5.0) and *High active* (DAS28 5.0 -). No pooling of data has been made, between the three groups, in order to give the reader the complete picture of the patients RA inflammation status in this study.

To value patients pain, their own perception of pain during the last week was measured by using visual analogue scale (VAS), results measured in mm. VAS is a visual analogue scale commonly used for pain perception.

Count of tender points was measured by using the fibromyalgia diagram.⁽³⁰⁻³²⁾ It is based on 18 standardized points on the human body. The evaluation was performed by a physical examination where digital pressure was placed to these 18 standardized points on the body. The score were measured from 0-18. Each tender point equals one point. The 18 points are visualised in picture 1.



Picture 1. Tender points. Open source <http://commons.wikimedia.org>

Statistics

The patient cohort was stratified by gender and by CV co-morbidity. Differences between the groups were analysed with Mann-Whitney U test. Values are presented as median and percentage. Spearman's correlation coefficient (ρ) was used to analyse the relationships between all used parameters. GraphPad Prism 6.01 was used for all statistical analyses and a P-value < 0.05 was considered statistically significant.

Ethics

The study is approved by the Ethical Review Board of West Göta County in Gothenburg, registration number 659-11, 2011-08-18.

Results

Clinical characteristics of the Rheumatoid Arthritis patient cohort

The study cohort consisted of 174 RA patients, 132 women and 42 men. Clinical and demographic characteristics of the patients are presented in Table 1a. This gender distribution is a 3:1 ratio (f:m), corresponding to the prevalence of RA patients in the population worldwide. In agreement with the inclusion criteria for the study, the patient cohort included subjects with established RA and the mean disease duration was above 8 years. Majority of the patients were of middle age, however all of them were within working age (Table 1a). Women and men were similar in age and in the duration and the activity of RA.

In this study we analyse the prevalence of known CV risk factors as; high BMI, smoking, hypertension, high levels of triglycerides, LDL, cholesterol and low levels of HDL. The inflammation and activity of RA, which is considered a major risk factor predisposing to CV disease in this patient group, was measured by DAS28.

Table 1A. Clinical characteristics of the RA patient cohort

| | Women (n=132) | Men (n=42) | Mann-Whitney U-test |
|--|------------------|------------------|---------------------|
| Age, years | 57 [45-63] | 59 [50-64] | |
| Disease duration, years | 8 [5-14] | 9 [6-18] | |
| DAS28 | 3.14 [2.06-4.11] | 2.64 [1.79-3.41] | |
| Remission (<3.2) | 68 (52%) | 27 (64%) | |
| Active (3.2 - <5.0) | 51 (38%) | 11(26%) | |
| High active (5.0 -) | 13 (10%) | 4(10%) | |
| VAS-pain, mm | 25 [11-48] | 37 [12-57] | |
| Tender points, n | 5 [2-9] | 2 [0-5] | p<0.0001 |
| CVC, n | 25 (19%) | 21 (50%) | OR 0.23 p=0.00016* |
| Hypertension without additional riskfactors | 18 | 12 | |
| Statins | 3 | | |
| ASA/Warfarin | 1 | 1 | |
| Stroke/MI + ASA | 1 | 2 | |
| Hypertension+statins | 1 | | |
| Hypertension+ASA/Warfarin+Statins | | | |
| Hypertension+ASA/Warfarin | | 5 | |
| Hypertension+ASA/Warfarin+Statins+Stroke/MI | | 1 | |

Data are presented as median [25-75 percentile]

* Women with CVC in relation to women without CVC compared to men with CVC in relation to men without CVC (The odds ratio is the ratio of the odds of the outcome in the two groups.)

Cardiovascular co-morbidity

The CV comorbidity in this study was defined by the presence of history of major CV events as well as medications for hypertension, anticoagulants (warfarin or Acetylsalicylic acid) and statins. Only two major CV events were reported in the study – one stroke and one myocardial infarction. Additionally, 40/174 (23%) patients had hypotensive drugs, 10/174 (6%) used anti-coagulants and 8/174 (5%) used statins. In this study it was found that 25 women (19%) had one of these CV risk factors, compared to 21 men (50%), indicating that women had 4.28 times lower (OR 0.23, [CI 95% 0.11-0.49]) prevalence of self-reported CV co-morbidity compared to men. Furthermore, 15% of the women in this study used hypotensive treatment compared to 47.6% of the men. This indicates that it was a lower likelihood that women used hypotensive treatment (OR 0.19, [CI 95% 0.09-0.42]) compared to men who participated in this study.

Women in this study had significantly lower BMI values compared to men (Tables 2 and 3). The median BMI for women was within the range of normal weight, while BMI for men was within the overweight group. Furthermore, women had significantly better pattern of blood fat values, lower levels of triglycerides compared to men and higher levels of HDL, while the levels of cholesterol were comparable in men and women. Low triglycerides and high HDL correspond to lower CV risk. Only 11.5% (20/174) of the patients reported to be current smokers, with a slightly higher prevalence among women compared to men (Table 1A).

Rheumatoid arthritis activity, treatment and pain perception

The participants of this study had low median disease activity of RA measured by DAS28 (Table 1A). However, 48% of the women had active or high RA (DAS28 >3.2), while the majority of men (64%) were in remission.

The anti-rheumatic treatment may potentially be a CV risk factor. According to the inclusion criteria, 87% of women and 93% of men were treated with MTX at the time of enrolment in the study. The dose of MTX per week was similar for women and men, between 5-25 mg/week. Remaining 10 patients have a temporary pause in their MTX treatment due to recent surgery or recurrent infection. In addition, 38% of the women and 50% of men were treated with biological drugs in combination to methotrexate. Furthermore, 11% of women and 17% of men used oral corticosteroids. (Table 1B)

Table 1B. Anti-rheumatic treatment in women and men

| Drugs and no. of users | Women | Women | All | Men | Men | All |
|-------------------------|-----------------|------------------|----------------|----------------|------------------|-------------|
| | No CVC n=107 | With CVC n=25 | Women n=132 | No CVC n=21 | With CVC n=21 | Men n=42 |
| Methotrexate | 97 (91%) | 20 (80%) | 117 (89%) | 18 (86%) | 21 (100%) | 39 (95%) |
| Biological drugs | 41 (38%) | 9 (36%) | 50 (38%) | 10 (48%) | 11 (52%) | 21 (50%) |
| Prednisolone | 13 (12%) | 1 (4%) | 14 (11%) | 4 (19%) | 3 (14%) | 7 (17%) |

Since pain is one of the major symptoms for RA patients, we investigated the perception of pain. In this study, women had significantly higher number of tender points ($p < 0.0001$) than men. However, when the VAS-pain was applied, no significant differences were reported between women and men.

Due to the objective differences in the prevalence of CV co-morbidity and for the CV risk factors found between the women and men in this study, we proceeded with separate analysis within each gender.

Cardiovascular co-morbidity in women

A total of 132 women participated in the study, 107 (81.1%) of them had no CV co-morbidity and 25 (18.9%) reported CV co-morbidity (Table 2A).

Table 2A. Cardiovascular co-morbidity in RA women

| | No CVC (n=107) | CVC (n= 25) | Mann-Whitney U-test |
|--------------------------------|-------------------|------------------|------------------------|
| Age, years | 55 [43-63] | 60 [56-65] | p=0.004 |
| Disease duration, years | 7 [4-12] | 8 [6-19] | |
| BMI, kg/m² | 24 [21.7-26.6] | 27.2 [25.0-29.8] | p=0.0003 |
| Cholesterol, mmol/L | 5.4 [4.5-5.9] | 5.5 [4.8-6.2] | |
| Triglycerides, mmol/L | 0.86 [0.66-1.10] | 1.2 [0.75-1.70] | p=0.002 |
| HDL, mmol/L | 1.8 [1.5-2.1] | 1.6 [1.4-2.1] | |
| LDL, mmol/L | 3.2 [2.5-3.8] | 3.4 [2.8-3.95] | |
| Current smokers, n (%) | 18 (17%) | 2 (8%) | |
| DAS28 | 2.97 [2.03-4.03] | 3.47 [2.81-4.62] | |
| Remission (<3.2) | 58 (54%) | 10 (40%) | |
| Active (3.2 - <5.0) | 40 (37%) | 11 (44%) | |
| High active (5.0 -) | 9 (8%) | 4 (16%) | |
| VAS-pain, mm | 25 [11-48] | 26 [10-48] | |
| Tender points, n | 5 [2-9] | 6 [3-10] | |

Data are presented as median [25-75 percentile]

In this study, women without CVC were significantly younger than women with CVC (p=0.004), which is in agreement with known increase in CVC with age. The groups were similar in the duration of RA disease but women with CVC tended to have higher disease activity.

Cardiovascular co-morbidity in RA women

As seen in table 2A, women without CVC had lower BMI as well as lower triglycerides than women with CVC. Both of these markers are associated with the increased risk of developing CVD. However, no significant differences were found in these groups of women when

comparing the blood levels of cholesterol, HDL and LDL. A correlation was found in women without CVC between cholesterol and HDL ($\rho=0.27$, $p=0.015$) as well as between cholesterol and disease duration ($\rho=0.29$, $p=0.01$). No such correlations were found in women with CVC. There were no significant differences when comparing smoking habits. (Table 2A)

Rheumatoid arthritis activity, treatment and pain perception in RA women

In this study, 45% of women without CVC had active or high active RA measured by DAS28 above 3.2, in contrast to 60% of the women with CVC. Furthermore, there was a tendency to lower DAS28 among women without CVC as they had a median value of 2.97 and women with CVC had a median value of 3.47.

In agreement with the inclusion criteria, most women used MTX, as a monotherapy or in combination with biological drugs (91% of the women without CVC compared to 80% of the women with CVC). Oral corticosteroids were used by 12% of women without CVC and in 4% of women with CVC. (Table 1B)

The two groups reported similar pain perception; no significant difference was found when comparing VAS or the number of Tender points. Since RA activity may influence the perception of pain, we analysed correlation between DAS28 and VAS and DAS28 and TP. A correlation was found between DAS28 and VAS ($\rho=0.35$, $p=0.002$) as well as between DAS28 and tender points ($\rho=0.45$, $p<0.0001$) in women without CVC. However, this link was not seen in women with CVC. To conclude, in women without CVC, increasing DAS28 correlate with increasing valued perception of pain, when using VAS-scale and tender-points. Table 2B depict increasing VAS along with increasing DAS28, in women without CVC.

Table 2B. Correlation of Disease activity and VAS in RA women

| | CVC | No CVC | CVC | No CVC | CVC | No CVC |
|-------------------|-----------|--------|-------------|-------------|-------------|--------|
| DAS28 | <3.2 | <3.2 | 3.21 – 4.99 | 3.21 – 4.99 | >5 | >5 |
| | Remission | | Active | | High active | |
| VAS median | 11.5 | 17.5 | 33 | 31.5 | 25.5 | 64 |
| 0-15, n | 6 | 26 | 3 | 8 | 1 | 1 |
| 16-46, n | 3 | 22 | 4 | 21 | 2 | 2 |
| 47-100, n | 1 | 10 | 4 | 11 | 1 | 6 |

Cardiovascular co-morbidity in men

Within this study a total number of 42 male participants were included; 21 of them had CVC and 21 did not. The comparison between the groups of men without CVC and men with CVC demonstrated a significant difference in age. Men without CVC were in average twelve years younger than men with CVC. Men without CVC were middle aged but men with CVC were close to the age of retirement. The groups were similar in the duration of RA disease.

Table 3A. Cardiovascular co-morbidity in RA men

| | No CVC n=21 | CVC n=21 | Mann-Whitney U-test |
|--------------------------------|------------------|------------------|------------------------|
| Age, years | 51 [41-62] | 63 [58-65] | p=0.0089 |
| Disease duration, years | 8 [4-15] | 9 [6-22] | |
| BMI, kg/m² | 27 [23.3-30.9] | 28.4 [25.5-29.3] | |
| Cholesterol, mmol/L | 5.3 [4.3-6.1] | 5.2 [4.3-5.9] | |
| Triglycerides, mmol/L | 0.99 [0.76-1.60] | 1.10 [0.87-2.20] | |
| HDL, mmol/L | 1.5 [1.2-1.8] | 1.3 [0.98-1.55] | |
| LDL, mmol/L | 3.5 [2.7-4.2] | 3.2 [2.45-4.15] | |
| Current smokers, n (%) | 2 (10%) | 3 (14%) | |
| DAS28 | 2.67 [1.91-3.34] | 2.42 [1.73-4.44] | |
| Remission (<3.2) | 14 (67%) | 13 (62%) | |
| Active (3.2 - <5.0) | 7 (33.3%) | 4 (19%) | |
| High active (5.0 -) | 0 | 4 (19%) | |
| VAS-pain, mm | 35 [10-61] | 37 [12-51] | |
| Tender points, n | 1 [0-5] | 2 [1-5] | |

Data are presented as median [25-75 percentile]

Cardiovascular co-morbidity in RA men

In this study, men without CVC and men with CVC were similar with respect to the traditional CV risk factors, BMI, smoking habits and the pattern of blood fat measured by the levels of cholesterol and triglycerides (Table 3A). Correlations were found between cholesterol and HDL ($\rho=0.55$, $p=0.015$) as well as between cholesterol and disease duration ($\rho=0.46$, $p=0.049$) in men without CVC. No correlations were found between these variables in men with CVC.

Rheumatoid arthritis activity, treatment and pain perception in RA men

The disease activity of RA, measured by the cumulative index DAS28, indicated that most of the men in this study had a remission of their RA disease. No significant difference in DAS28 was found between men without CVC and men with CVC (Table 3A). None of the men without CVC had high active RA compared to 19% of men with CVC.

RA treatment was similar between the groups, regardless of CVC, 86% of men without CVC and 100% of the men with CVC were treated with MTX. Half of the RA men were treated with biological drugs, 48% of the men without CVC and 52% of the men with CVC. Furthermore, less than 1/5 of the men used oral corticosteroids. (Table 1B)

In this study, the perception of pain according to VAS and to the number of tender points was similar between the men without CVC and the men with CVC (Table 3A). However, when dividing RA patients in to three groups by their disease activity, the patients reported higher pain perception (VAS) in correlation with higher DAS28 (Table 3B). Furthermore, men with CVC had a clear correlation between DAS28 and VAS ($\rho=0.48$, $p=0.038$), and between DAS28 and tender points ($\rho=0.55$, $p=0.014$). No such correlations were found within the group of men without CVC.

Table 3B. Correlation between disease activity and VAS in RA men

| | CVC | No CVC | CVC | No CVC | CVC | No CVC |
|-------------------|-----------|--------|-------------|-------------|-------------|--------|
| DAS28 | <3.2 | <3.2 | 3.21 – 4.99 | 3.21 – 4.99 | >5 | >5 |
| | Remission | | Active | | High active | |
| VAS median | 16 | 21 | 38.5 | 46 | 55 | 0 |
| 0-15, n | 6 | 7 | 0 | 2 | 0 | 0 |
| 16-46, n | 4 | 2 | 4 | 2 | 2 | 0 |
| 47-100, n | 3 | 5 | 0 | 3 | 2 | 0 |

Discussion

Cardiovascular co-morbidity

A large amount of all RA patients have CV comorbidity.⁽¹¹⁾ Intriguingly, a clearly significant difference was found in this study, when comparing the number of women and men with CVC. 19% of women and 50% of men reported to have CV co-morbidity, indicating that women had four times lower self-reported CV co-morbidity. The reason for this difference between women and men could be that men tend to develop CV diseases 10-20 years earlier than women do.⁽¹⁴⁾ This could indicate that this difference, in this study cohort, is caused by gender.

The typical CV risk factors include dyslipidaemia, diabetes mellitus, hypertension and higher body mass index (BMI).⁽⁷⁾ Women with CVC do follow some of this traditional pattern of risk factors for CVC as they had higher: triglycerides, BMI and age than women without CVC. In line with other findings, in women triglycerides are one of the most important values when calculating risk factors for both total mortality and death from myocardial infarction.⁽¹⁵⁾

A tendency to higher inflammatory parameters was seen in women with CVC who has higher BMI, triglycerides and age than women without CVC. Studies have shown that increasing BMI leads to difficulties to reach disease remission in RA.⁽¹⁸⁾

Men in this study had more risk factors for developing CV co-morbidity because of their high BMI, high triglycerides as well as low HDL compared to women. In line with other findings, men in this study had many risk factors for developing cardiovascular diseases.⁽⁸⁾ Moreover, men without CVC and men with CVC were similar with respect to BMI, smoking habits, and the pattern of blood fat measured by the levels of cholesterol and triglycerides, indicating similarity in risk for developing CVD. One can hypothesize that men without CVC in this

study could be underdiagnosed since they are comparable with men with CVC. When comparing with the Swedish population in general, within the group of 55-64 years, 20.3% of the women have hypertension and 23.2% of the men.⁽³³⁾ In this study, 15% of the women reported the use of medicaments for hypertension versus as much as 47.6% of the men. Men in this study have more developed CVC than the male population in average as they have higher incidence of hypertension. One could speculate if their RA could have affected the development of CVC. Men in this study have higher incidence of use of medicament treating hypertension than men in general, in this age category, Studies have shown that RA patients have a 50% increased risk of mortality due to CVC.^(34, 35)

Rheumatoid arthritis activity and treatment

To participate in the study one had to be treated with MTX. That explains why so many of the participants have reported their use of this medicament. Due to the fact that some of the participants had a temporary pause in their MTX treatment, not 100% used this medicament at the moment of investigation.

There were no significant differences when comparing use of medicaments between women and men. However, 38% of the women without CVC and 36% of women with CVC used biological drugs, compared to approximately 50% within men as a group. Men tend to use both biological drugs and corticosteroids more frequently than women did.

The development of CVC in Rheumatoid Arthritis is caused by an underlying inflammation, the use of RA medicament as well as traditional cardiovascular risk factors.⁽⁸⁾ It is believed that Methotrexate and biologicals could reduce the risk of CVC while corticosteroids have harmful effect on blood-lipids as well as blood pressure.⁽⁸⁾ Men in this study did use both more biological drugs and corticoids than women. As much of 50% of men in this study had CVC but the majority of men (64%) were in remission in their RA. Further studies in how RA

treatment affects patients in their development of both CVC and RA would be interesting. Moreover, a research investigating when patients started with their anti-rheumatic treatment would be of great interest since early start of anti-rheumatic treatment is associated with reduced CV risk.⁽⁸⁾

Pain perception

High disease activity is believed to be associated with RA pain.⁽²⁰⁾ In this study this is true for women without CVC and men with CVC as increasing DAS28 correlate with increasing valued perception of pain, when using VAS-scale and tender-points. Increasing VAS along with increasing DAS28 is true for all patients except for women with CVC with high active RA. However, the group of women with CVC and high active RA consisted of only four participants. None of the men appertained to the group of men without CVC and high active RA. Further research regarding pain perception and disease activity with additional patients would be of great interest to get manifest conclusions.

When comparing participants with and without CVC, both women and men in both groups perceived pain very similar. No differences were found when comparing VAS or Tender points between these groups. This might indicate that cardiovascular diseases do not effect the sensation of pain. However, women tend to value their pain much higher than men did concerning palpation of certain areas of the body, tender points (TP). When comparing tender points, men had significant lower amount of tender points than women ($p < 0.0001$). In line with other findings, it has been shown that women are more sensitive when graduating tender points then men are and that men and women perceive pain differently.^(23, 24)

Conclusion

In this study, it has been found that fewer women than men reported cardiovascular co-morbidity. These findings reflect the general population since women tend to develop CVC later than men do.

Established CV risk factors are for example dyslipidaemia, hypertension, high BMI and high age. Women in this study who reported CVC do follow these traditional patterns of risk factors. However, even though half of the men reported CVC, men without CVC and men with CVC were similar when comparing risk factors for developing CVC. No significant distinctions were found when comparing neither risk factors nor inflammation parameters between men without CVC and men with CVC.

In line with other findings, women and men valued their pain very differently when graduate tender points. However, no differences were found when comparing VAS-pain. Furthermore, similar pain perception was reported from both women and men without CVC as well as women and men with CVC. To conclude, CVC was not associated with increased pain perception in RA patients.

Methodological considerations

This is an observational study. Observational studies is used for investigate possible relationships between exposure and outcomes. Moreover, this cross-sectional study has analysed the situation at present and it is not prospective. No control group was used in this study. This observational study was instead concentrated on finding differences or similarities within RA patients who receive comparable treatment. As diabetes mellitus occur more frequently in patients with RA and is also a well-established cardiovascular risk factor, one can argue for include diabetes mellitus as a definition of CVC.⁽³⁶⁾ On the other hand,

cardiovascular morbidity and mortality in RA patients is high and comparable to patients with diabetes mellitus.⁽⁶⁻⁸⁾ Therefore, it could have been an opportunity to use patients with diabetes mellitus as a control group.

In this study, patients from the Methotrexate register were used. They participated voluntarily and filled in a self-assessment questionnaire, underwent a physical examination and left a laboratory test with blood sampling. All patients fulfilled the classification criteria of RA proposed by ACR 1987.⁽²⁶⁾ 1987 ACR criteria are believed to have higher specificity especially in patients aged > 60 years in order to diagnose RA, than the newer 2010 ACR/EULAR criteria. Moreover, 1987 ACR criteria are suggested to predict a more erosive disease whereas the 2010 criteria classify more patients with RA and at an earlier phase of the disease.^(37, 38)

The argument for using patients treated with methotrexate is because this medicament is the most commonly used RA treatment and constitute the basis in RA therapy. Moreover, patients who receive methotrexate have severe RA and are in need of sufficient treatment.

Information concerning patient's medicaments came from the patients and was not double-checked. This could lead to inaccurate information as patients could forget or misunderstand questions. However, unfilled questionnaires with ambiguous information was not included in the study.

Furthermore, blood samples were taken at only one occasion and no considerations were taken to temporary infections or variables that could have intrude the data.

Since the number of patients included in this study is somewhat limited, more studies including larger numbers of patients have to be performed and the results in this study need to be verified by further studies. Moreover, especially the number of men was limited and the conclusions from the study are therefore more relevant for women.

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Abbreviation list

| | |
|--------|---------------------------------------|
| BMI | Body Mass Index |
| CRP | C-reactive protein |
| CVC | Cardiovascular co-morbidity |
| DAS28 | Disease Activity Score |
| ESR | Erythrocyte sedimentation rate |
| HDL | High-density lipoprotein |
| LDL | Low-density lipoprotein |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| RA | Rheumatoid arthritis |
| TP | Tender Points |
| VAS | Visual analogue scale |

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Populärvetenskaplig sammanfattning

Ledgångsreumatism (eg. Reumatoid artrit) är en kronisk autoimmun sjukdom som cirka en procent av Sveriges befolkning har och sjukdomen är ungefär tre gånger så vanlig hos kvinnor som hos män. Inflammationen som kommer av sjukdomen leder till värk, smärta och stelhet i leder men även andra organ kan påverkas. Påverkan på lederna sker symmetriskt i kroppen och det är alltid flera leder som påverkas.

Det har visat sig att patienter med ledgångsreumatism lider av högre risk att drabbas av hjärt-kärlsjukdomar (jämförbart med risken hos dem som lider av sockersjuka (diabetes mellitus)). Kända riskfaktorer till hjärt-kärlsjukdom hos patienter med ledgångsreumatism är blodfettrubbning, sockersjuka, högt blodtryck samt ökat kroppsmasseindex (Body Mass Index, BMI). Även behandlingseffekter skulle kunna vara en förklaring till den ökade risken för hjärt-kärlsjukdom med detta är ännu inte helt klarlagt.

En studie som undersöker ovanstående samband ytterligare är därför av stor betydelse då det skulle kunna leda till att bättre förebygga riskfaktorer för hjärt-kärlsjukdom samt ett bättre omhändertagande av dessa patienter.

Denna studie har analyserat sambanden mellan smärta, inflammation och hjärt-kärlsjukdomar in en grupp av patienter med diagnosticerad ledgångsreumatism. Data har insamlats från Sahlgrenska Universitetssjukhusets Metotrexat register från 198 kvinnor och män med diagnosen ledgångsreumatism. Dessa data har undersökts bland annat med avseende på inflammationsmarkörer, självupplevd smärta, svullna och smärtande leder, historia av hjärt-kärlsjukdom, blodfetter, rökning samt kroppsmasseindex.

Resultatet i studien visar att 19 % av kvinnorna lider av eller upplevt någon hjärt-kärlsjukdom i jämförelse med 50 % av männen. Av de riskfaktorer som nämns ovan syns att män generellt

lider av större blodfettsrubbing än kvinnor och att de också har högre kroppsmasseindex. Vad gäller aktiviteten av sjukdomen visade studien att nästan 50 % av kvinnorna led av aktiv eller mycket aktiv ledgångsreumatism i jämförelse med männen där 64 % hade en sjukdom som stället var i avtagande fas, remission. Kvinnor uppgav också i större utsträckning än män att de hade mer smärta gällande ömmande punkter på kroppen.

Denna studie visar att kvinnor med hjärt-kärlsjukdom har signifikant högre kroppsmasseindex, är äldre och har högre triglycerider (blodfetter) än kvinnor utan hjärt-kärlsjukdom. Detta är faktorer av betydelse för utvecklingen av hjärt-kärlsjukdom. Vidare har 60 % av kvinnorna med hjärt-kärlsjukdom en aktiv eller mycket aktiv ledgångsreumatism i jämförelse med 45 % av kvinnorna utan hjärt-kärlsjukdom. 50% av männen hade redan utvecklat hjärt-kärlsjukdom även fast inga nämnvärda skillnader fanns mellan män utan hjärt-kärlsjukdom och män med hjärt-kärlsjukdom.

Då patienterna som deltog i denna studie var en del av Sahlgrenskas Metotrexat register behandlades de allra flesta med denna medicinering. Dock fanns skillnader mellan män och kvinnor gällande behandlingen med nyare biologiska läkemedel och kortison. 50% av männen behandlades med biologiska läkemedel till skillnad mot kvinnor där 38% hade dessa läkemedel. 17% av männen behandlades med kortison i jämförelse med 11% av kvinnorna.

Sammanfattningsvis visar således studien att kvinnor generellt har en mer aktiv sjukdom än män samt att kvinnor som har en hjärt-kärlsjukdom i större utsträckning också har en mer aktiv ledgångsreumatism. Större andel män än kvinnor led av hjärt-kärlsjukdom trots adekvat behandling och låg aktivitet i sin ledgångsreumatism. Detta kan antas bero på att män generellt sett utvecklar hjärt-kärlsjukdom flera år tidigare än kvinnor.

För att bringa ytterligare klarhet i varför dessa samband föreligger och vad vi kan göra åt dem behövs ytterligare forskning inom området. Detta är mycket viktigt för att öka förståelsen och

kunskapen kring ledgångsreumatism då det leder till ett bättre omhändertagande av patienterna samt att nya behandlingsriktlinjer kan introduceras. Genom forskning finns förutsättningar för att patienter som lider av ledgångsreumatism med eller utan hjärt-kärlsjukdom kommer ha få ett allt friskare och välmående liv.