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Original article

Increased cardiovascular risk factors in different rheumatic diseases compared with the general population

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Abstract

Objectives. To study the prevalence of cardiovascular risk factors among patients attending a rheumatology outpatient clinic in comparison with the general population.

Methods. Cross-sectional comparison between a rheumatic outpatient cohort of consecutive patients ($n = 1233$) between 36 and 75 years of age attending the Arthritis Center Twente (ACT) in the year 2009: RA ($n = 546$), gout ($n = 129$), OA ($n = 168$), CTD ($n = 85$), PMR ($n = 91$) and chronic localized or generalized pain syndromes (CPSs; $n = 214$) and a random sample from a long-lasting population-based health study in the Netherlands ($n = 4523$). The main outcome measures were hypertension (systolic blood pressure $\geqslant 140$ mmHg and/or a diastolic blood pressure $\geqslant 90$ mmHg and/or the use of antihypertensive medication), abnormal cholesterol profile (total cholesterol $\geqslant 6.5$ mmol/l, and/or high-density lipoprotein < 0.9 mmol/l and/or use of lipid lowering medication), overweight (BMI $\geqslant 25$ kg/m^2), obesity (BMI $\geqslant 30$ kg/m^2) and cigarette smoking habits (self-reported current smoking).

Results. Compared with the general population, patients with rheumatic diseases have a significantly higher prevalence of hypertension ($P_{ACT} = 68\%$, $P_{general} = 57\%$), being overweight ($P_{ACT} = 72\%$, $P_{general} = 62\%$), obesity ($P_{ACT} = 30\%$, $P_{general} = 17\%$) and cigarette smoking ($P_{ACT} = 26\%$, $P_{general} = 21\%$). The worst risk profile was found in gout patients, with higher prevalence of all cardiovascular risk factors studied.

Conclusion. Lifestyle-associated potentially modifiable cardiovascular risk factors are over-represented along the whole spectrum of chronic rheumatic diseases, and not only in RA, as suggested by preceding studies.

Key words: cardiovascular risk, arthritis, gout, osteoarthritis, pain syndromes.

CLINICAL SCIENCE

Introduction

Chronic rheumatic and cardiovascular diseases share common pathophysiological factors: immobility, obesity, inflammation and smoking. Diseases such as RA, gout, PMR and CTD are characterized by chronic or intermittent inflammation, and are treated with anti-inflammatory drugs. The relationship between different chronic rheumatic and cardiovascular diseases has not been studied. Most research has been done on increased cardiovascular morbidity and mortality in RA patients [1–4]. The high prevalence of cardiovascular disease in RA might be explained by clustering of lifestyle-associated cardiovascular risk factors, chronic inflammation and/or the use of medication, such as non-steroidal anti-inflammatory drugs and disease-modifying anti-rheumatic drugs. Other rheumatic diseases have also been associated with increased cardiovascular risk. Gout may be part of the metabolic syndrome, i.e. abdominal adiposity, glucose intolerance, hypertension and dyslipidaemia, a complex of abnormalities accompanying unhealthy Western lifestyles associated with increased cardiovascular morbidity and excess mortality [5–7]. Some small studies in PMR have

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found an increased prevalence of arteriovascular disease [8–10]. Vascular dysfunction and accelerated atherosclerosis are established features of SLE especially when accompanied by anti-phospholipid antibodies, and have also been observed in other CTDs, such as SSc [11–13]. The impact of traditional cardiovascular risk factors on CTD-associated cardiovascular complications remains uncertain.

Less is known about rheumatological disorders without systemic inflammation, such as OA and chronic widespread pain syndromes (CPSs). Recent data have suggested these may also be associated with cardiovascular disease, possibly because of the high prevalence of lifestyle-associated risk factors [14, 15]. The aim of this study was to compare the prevalence of traditional cardiovascular risk factors in different rheumatic diseases with that in the general population.

Methods

Data sources

Data for this study were obtained from two databases on lifestyle-associated cardiovascular risk factors in individuals from the same geographical region in the eastern part of the Netherlands. Data recorded include demographics, medical diagnoses, cigarette smoking habits, laboratory test results, recordings of height, weight and blood pressure and current drug prescriptions. The databases are briefly described later in the text.

Arthritis Center Twente cardiovascular disease project

In 2009 the Arthritis Center Twente (ACT) established a protocol of cardiovascular screening as part of its standard of care. After 1 year of screening, the database contained the completed data of 1500 patients who were representative of the entire outpatient population. Patients were categorized into six groups by their primary diagnosis: (i) RA, (ii) gout, (iii) OA, (iv) CTDs; SLE, SSc, SS, systemic vasculitis), (v) PMR and/or arteritis temporalis and (vi) CPS: fibromyalgia, non-inflammatory tendinopathies, hypermobility and non-inflammatory arthralgia). Data collection on cardiovascular risk factors took place by standardized physical examination and fasting blood sample at one regular visit to the outpatient clinic. RA disease activity was measured by the DAS-28. The protocol for data collection and storage was approved by the institutional review board.

Doetinchem cohort study (fourth measurement round: 2003–2007)

Data from the general population were derived from the fourth measurement round of the Doetinchem Cohort, which was conducted as part of a long-lasting, population-based health study (DCS). All participants gave written informed consent, and the study was approved according to the guidelines of the Declaration of Helsinki by the Medical Ethics Committee of the Netherlands Organization of Applied Scientific Research. Data collection took place by standardized physical examination by trained personnel during a visit to the municipal health service, a non-fasting blood sample and self-reported questionnaires for demographic and lifestyle characteristics, as described previously [16].

Study population

For each database, individuals were eligible for inclusion when aged 36–74 years at the time of examination. In all, 1233 patients from the ACT cardiovascular disease (ACT-CVD) cohort and 4523 individuals from the DCS met this criterion.

Cardiovascular risk factor measurements in both study protocols

Cardiovascular risk factors assessed during physical examination were BMI and blood pressure. In both study protocols, height and weight were measured barefoot, wearing light clothes only. At the ACT outpatient clinic, body weight was measured by mechanical scales to the nearest 1 kg, body weight measurement in the DCS was by balance beam scale to the nearest 0.5 kg. To adjust for light indoor clothing, 1 kg was subtracted from the measured weight. Height measurement procedures were the same in both study protocols, using a wall-mounted stadiometer to the nearest 0.5 cm. BMI was calculated as the ratio of weight (kg) and squared height (m). Overweight was defined as a BMI $\geqslant 25\,kg/m^2$, obesity as a BMI $\geqslant 30\,kg/m^2$.

Readings of systolic and diastolic blood pressure were obtained at rest on the right arm with the patient in a sitting position using a calibrated blood pressure instrument. Hypertension was defined as a systolic blood pressure $\geqslant 140$ mmHg and/or a diastolic blood pressure $\geqslant 90$ mmHg and/or the use of anti-hypertensive medication. Measurements of cholesterol values were performed in two laboratories, both using standardized CHOD-PAP and HDL-C third-generation assays for assessment of total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol, respectively. Hypercholesterolaemia was defined as TC $\geqslant 6.5$ mmol/l and/or use of lipid-lowering medication, low HDL as HDL cholesterol values <1.0 mmol/l.

Statistical analysis

The prevalence of cardiovascular risk factors in patients with rheumatic diseases and in control subjects was presented as descriptive statistics (mean or percentage prevalence) adjusted for differences by sex and age. Differences between patients with rheumatic diseases and control subjects were tested with analysis of variance (for continuous cardiovascular risk factors) or logistic regression analyses (for dichotomous cardiovascular risk factors). Differences in dichotomous risk factors between patients and control subjects were also presented by odds ratios (ORs) with 95% CIs. Data analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

The overall rheumatology outpatient population

Both populations showed comparable distributions of age, women being slightly over-represented in the ACT-CVD cohort (ACT-CVD 62% *vs* DCS 53%; Table 1). Most patients were diagnosed with RA (546), followed by CPS (214; 34 fibromyalgia, 49 non-inflammatory tendinopathies, 131 non-inflammatory arthralgia), OA (168), gout (129), PMR (91) and CTDs (85; 28 SLE, 18 SSc, 14 SS, 25 systemic vasculitis). When comparing the complete ACT-CVD cohort with the DCS cohort, most risk factors were increased, with a significantly higher prevalence of overweight, current smoking and hypertension (Table 2). Hypertension was uniformly increased among all specific rheumatic diseases, as were measurements of weight, i.e. overweight and obesity, with the exception of the group of CTDs. In specific diseases, the prevalence of other risk factors differed substantially as compared with the DCS cohort (Tables 2 and 3, Fig. 1); this is discussed in the following subsections.

RA

RA patients (341 women and 205 men, mean disease duration 81 months, 69% in remission according to DAS-28 score $\leqslant 2.6$) had a significantly higher prevalence of overweight, obesity and hypertension compared with the DCS cohort. RA patients were characterized by an increased prevalence of current smoking.

Gout

In gout patients (116 men and 13 women, 76% treated with uric acid-lowering medication), all risk factors measured were significantly more prevalent compared with the DCS cohort. In comparison with the DCS cohort, these patients showed the highest prevalence of overweight and obesity. Gout was the only disease with unfavourable TC/HDL ratios compared with the DCS cohort, whereas gout patients were also significantly more frequently treated with lipid-lowering drugs.

OA

OA patients (131 women and 37 men) had a significantly higher prevalence of hypertension compared with the DCS cohort. Furthermore, OA patients were characterized by a high prevalence of overweight and obesity.

CTD

Patients with CTD (63 women and 22 men) did not differ significantly from the DCS cohort in lifestyle-associated cardiovascular risk factors, except for a lower, more favourable mean TC/HDL ratio.

PMR

PMR patients (57 women and 34 men) had significantly increased frequencies of obesity and hypertension compared with the DCS cohort.

CPSs

CPS patients (158 women and 56 men) had significantly increased prevalence of current smoking, overweight, obesity and hypertension compared with the DCS cohort. Statins were significantly more frequently prescribed in CPS patients compared with the DCS cohort, and TC values were significantly more favourable.

Discussion

This study shows that cardiovascular risk factors are over-represented in all the rheumatic diseases studied. There may be different patterns of risk factors in specific rheumatic diseases. Overweight and hypertension were consistently present in all rheumatic diseases studied. RA patients are further characterized by a high prevalence of smoking, whereas gout patients show an increase in all risk factors measured.

RA being associated with current smoking is in line with the concept of cigarette smoking in the pathogenesis of RA [17–19]. Cigarette smoking is a major health problem in RA, as it not only affects the disease itself, but also the development of RA's most prevalent fatal comorbidities,

Table 1 Age and sex distribution of study populations

	DCS ($n = 4523$)	All rheumatic diseases ($n = 1233$)	By specific disease					
			RA ($n = 546$)	Gout ($n = 129$)	OA ($n = 168$)	CTD ($n = 85$)	PMR ($n = 91$)	CPS ($n = 214$)
Age group, years, %								
30-40	6.2	6.1	5.7	4.7	1.8	10.6	0	12.2
40-50	25.9	21.4	22.2	13.2	16.7	28.2	1.1	34.1
50-60	35.2	31.1	30.6	27.9	38.1	29.4	18.7	35.1
60-70	24.0	29.3	28.8	41.1	32.7	25.9	45.1	15.4
70-80	8.7	12.1	12.8	13.2	10.7	5.9	35.2	3.3
Sex, %								
Men	47.4	38.1	37.6	89.9	22.0	25.9	37.4	26.2
Women	52.6	61.9	62.5	10.1	78.0	74.1	62.6	73.8

TABLE 2 Cardiovascular risks among patients with rheumatic diseases and controls

Risk factor	DCS ($n = 4523$)	All rheumatic diseases ($n = 1233$)	By specific disease					
			RA ($n = 546$)	Gout ($n = 129$)	OA ($n = 168$)	CTD ($n = 85$)	PMR ($n = 91$)	CPS ($n = 214$)
Current smoking, %	20.5	25.9*	28.1*	26.4	20.6	19.0	22.6	27.0
Ever smoking, %	62.7	64.6	67.3	74.4*	61.1	61.7	54.7	64.4
Systolic BP, mmHg, mean	135.7	143.4*	141.6*	149.2*	146.7*	137.6	148.8*	142.1*
Diastolic BP, mmHg, mean	85.0	84.1*	84.2	86.9*	84.2	82.0*	81.3*	84.1
BP > 140/90 mm Hg, %	41.8	57.9*	55.0*	71.3*	60.8*	50.6	63.0*	59.3*
Use of antihypertensive medication, %	16.6	28.3*	25.2*	43.4*	32.4*	28.7*	30.1*	24.5*
Hypertension (BP > 140/90 mmHg or med), %	56.0	65.7*	62.2*	83.0*	68.1*	62.8	68.8*	66.6
TC, mmol/l, mean	5.58	5.29*	5.28*	5.21*	5.53	5.11*	5.35*	5.24*
HDL cholesterol, mmol/l, mean	1.43	1.45	1.45	1.14*	1.47	1.53*	1.70*	1.46
TC/HDL ratio, mean	4.2	4.0*	3.9*	4.9*	4.0*	3.6*	3.3*	3.8*
High TC (>6.5 mmol/l), %	16.3	10.4*	8.7*	13.2	15.9	7.4*	11.5	9.1*
Low HDL cholesterol (<0.9 mmol/l), %	8.2	8.7	8.8	18.6*	8.1	8.9	3.2	6.9*
Use of lipid-lowering medication, %	10.1	12.1*	8.6	22.5*	13.1	11.7	17.3*	14.1
Abnormal cholesterol profile (including med), %	31.5	28.5	20.0*	46.5*	35.5	25.1	31.4	26.9*
BMI, kg/m^2, mean	26.6	28.0*	27.3*	30.7*	29.1*	27.1	28.0*	27.7*
Overweight (BMI $\geqslant$25 kg/m^2), %	61.9	72.2*	68.3*	93.8*	80.5*	64.4	65.8	74.1*
Obesity (BMI $\geqslant$30 kg/m^2), %	17.3	28.2*	22.6*	48.1*	34.0*	24.4	26.6*	28.0*

Figures adjusted for differences in sex and age. *$P < 0.05$. BP: blood pressure.

chronic obstructive pulmonary disease and cardiovascular events [3, 20]. Cholesterol profiles in RA compared favourably with the general population. This seems remarkable because previous studies in predominantly untreated patients showed increased dyslipidaemia in RA [21]. However, cholesterol values have been shown to decrease with lower disease activity and levels of inflammation. Our study included treated patients with average low disease activity [22]. When looking at the number of risk factors, gout patients showed the worst traditional cardiovascular risk profile compared with the general population. Gout was characterized by increased prevalence of all the evaluated risk factors compared with the general population, and it was the only group with significantly increased prevalence of abnormal cholesterol profiles. Previous studies evaluating cardiovascular risk in hyperuricaemia and gout show conflicting results. Some show hyperuricaemia to be an independent risk factor for cardiovascular events and death; others find no such associations or only with gouty arthritis [23–26]. Gout and hyperuricaemia have also been associated with the metabolic syndrome, a complex of the individual cardiovascular risk factor overweight, hypertension, dyslipidaemia and diabetes [5–7]. These results are in line with previous studies on associations between the complex of metabolic cardiovascular risk factors called the metabolic syndrome and gout [5–7]. Other studies have shown associations between gout or serum uric acid levels and cardiovascular morbidity and mortality [23, 24, 27]. In the CTD group, none of the traditional cardiovascular risk factors was significantly increased compared with the general population. This seems remarkable because several diseases in this category have previously been associated with increased cardiovascular morbidity and mortality [11–13]. One explanation could be that cardiovascular disease in CTD is primarily the result of the disease itself, because of involvement of the vascular system, resulting in vascular dysfunction predisposing to cardiovascular events [28].

This is the first study evaluating cardiovascular risk factors across a broad spectrum of rheumatic diseases and comparing these with the general population. While interpreting these results, some limitations should be taken into account. The data on patients and the general population were extracted from two independent studies: the ACT-CVD cohort and DCS. Data collection in these studies took place over 6 years, and both were conducted in the same geographical region in the eastern part of the Netherlands. For this study, risk factors with equivalent measurement procedures were included. Because of limited registration of data on the use of medication in the DCS, only associations with the use of anti-hypertensives and lipid-lowering drugs could be evaluated.

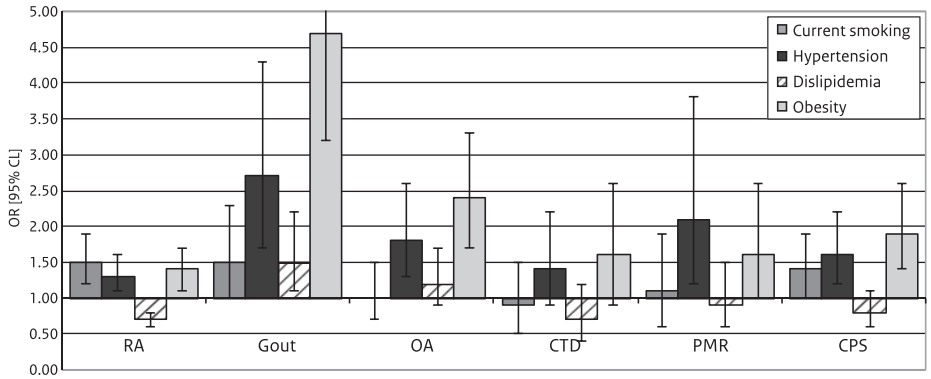
Blood pressure measurement instruments differed, which might have affected the comparison of blood pressure values between rheumatic diseases and the general population. Because original data were available, the same definitions of hypertension and dyslipidaemia could be applied in both cohorts. Laboratory measurements were performed in single laboratories at different

Table 3 Cardiovascular risk factors among patients with rheumatic diseases, OR (95% CI) versus controls

Risk factor	All rheumatic diseases ($n = 1233$)	By specific disease					
		RA ($n = 546$)	Gout ($n = 129$)	OA ($n = 168$)	CTD ($n = 85$)	PMR ($n = 91$)	CPS ($n = 214$)
Current smoking, %	1.3 (1.2, 1.6)*	1.5 (1.2, 1.9)*	1.5 (1.0, 2.3)*	1.0 (0.7, −1.5)	0.9 (0.5, −1.5)	1.1 (0.6, −1.9)	1.4 (1.0, 1.9)*
Ever smoking, %	1.1 (0.9, 1.2)	1.2 (1.0, 1.5)	1.3 (0.8, 1.9)	1.0 (0.7, 1.3)	0.9 (0.6, 1.5)	0.7 (0.4, 1.0)	1.1 (0.8, 1.4)
BP>140/90 mmHg, %	2.0 (1.7, 2.6)*	1.8 (1.5, 2.1)*	2.5 (1.7, 3.7)*	2.3 (1.7, 3.2)*	1.5 (0.9, 2.3)	2.5 (1.6, 4.0)*	2.1 (1.6, 2.9)*
Use of antihypertensive medication, %	2.0 (1.7, 2.3)*	1.7 (1.4, 2.1)*	3.6 (2.4, 3.4)*	2.4 (1.7, 3.4)*	2.2 (1.3, 3.6)*	1.8 (1.2, 2.8)*	1.8 (1.3, 2.5)*
Hypertension (BP>140/90 mmHg, incl. med), %	1.6 (1.4, 1.8)*	1.3 (1.1, 1.6)*	2.7 (1.7, 4.3)*	1.8 (1.3, 2.6)*	1.4 (0.9, 2.2)	2.1 (1.2, 3.8)*	1.6 (1.2, 2.2)*
High TC (>6.5 mmol/l), %	0.6 (0.5, 08)*	0.5 (0.4, 0.7)*	0.8 (0.4, 1.3)	1.0 (0.7, 1.5)	0.5 (0.2, 1.0)*	0.7 (0.4, 1.2)	0.5 (0.3, 0.8)*
Low HDL cholesterol (<0.9 mmol/l), %	1.1 (0.9, 1.4)	1.1 (0.8, 1.6)	1.8 (1.1, 2.8)*	1.0 (0.5, 2.1)	1.2 (0.5, 3.0)	0.3 (0.1, 1.3)	0.7 (0.4, 1.5)
Use of lipid lowering medication, %	1.2 (1.0, 1.50)*	0.8 (0.6, 1.1)	1.9 (1.2, 2.9)*	1.4 (0.9, 2.2)	1.2 (0.6, 2.5)	1.5 (0.9, 2.6)	1.6 (1.0, 2.6)*
Abnormal cholesterol profile (incl. med), %	0.9 (0.8, 1.0)*	0.7 (0.6, 0.8)*	1.5 (1.1, 2.2)*	1.2 (0.9, 1.7)	0.7 (0.4, 1.2)	0.9 (0.6, 1.5)	0.8 (0.6, 1.1)
Overweight, %	1.6 (1.4, 1.9)*	1.3 (1.1, 1.6)*	6.6 (3.2, −13.7)*	2.5 (1.7, −3.6)*	1.1 (0.7, −1.8)	1.2 (0.7, −1.9)	1.7 (1.3, 2.3)*
Obesity, %	1.9 (1.6, 2.2)*	1.4 (1.1, 1.7)*	4.7 (3.2, −6.7)*	2.4 (1.7, −3.3)*	1.6 (0.9, −2.6)	1.6 (1.0, −2.6)*	1.9 (1.4, 2.6)*

Figures adjusted for differences in sex and age. *$P < 0.05$. BP: blood pressure.

Fig. 1 Cardiovascular risks among rheumatic diseases.



Prevalence of cardiovascular risk factors in RA, gout, OA, CTD, PMR and CPS; ORs in comparison with the general population.

institutions for each study. Both laboratories were reference laboratories using the same standardized testing methods and participating in national calibration procedures. Therefore comparison of cholesterol measurements was regarded as justified.

Lastly, the DCS is a long-lasting population-based health study, and data for this study were taken from the fourth measurement round. The worried well, i.e. concerned individuals from a low-risk population who frequently seek contact with health care institutions, are usually over-represented in these studies, resulting in a relatively healthy sample. However, no selection for the population-based sample was made, and it also includes individuals with rheumatic diseases. Altogether, we expect that this might have caused a minor overestimation of the differences with rheumatic diseases.

Conclusions

In rheumatic diseases, the prevalence of cardiovascular risk factors is high. Overweight and obesity are almost

uniformly present. Gout has the most unfavourable risk profile, including the whole spectrum of traditional cardiovascular risk factors. Cigarette smoking is a highly prevalent health hazard in RA.

Rheumatology key messages

- Cardiovascular risk factors are increased in different rheumatic diseases.
- Specific rheumatic diseases may have different cardiovascular risk patterns.
- Gout is a flaming red flag for lifestyle-associated cardiovascular risk.

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