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ORIGINAL ARTICLE

Cardiac and cardiovascular morbidities in patients with psoriatic arthritis: a population-based case control study

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Abstract

Objective To assess the prevalence of risk factors associated with cardiovascular disease (CVD) and CVD-related morbidity in a large Middle-Eastern psoriatic arthritis (PsA) cohort.

Method A retrospective case control study was conducted using Israel's largest health care provider's patient database from 2000 to 2013. For each patient with PsA, 10 patients with no history of psoriasis or arthritis were matched for age and sex. Analysis of CVD-related risk factors and morbidity included hypertension (HTN), hyperlipidemia (HLD), diabetes mellitus type 2 (DM-2), obesity, smoking, ischemic heart disease (IHD), congestive heart failure (CHF), cerebrovascular accident (CVA), carotid artery disease, peripheral vascular disease (PVD), aortic aneurism, valvular heart disease (VHD), and cardiomyopathy. Statistical analysis was conducted using *t* test and chi-square tests as appropriate. Univariate and multivariable logistic regression models assessed the association between PsA and CVD-related risk factors and morbidity.

Results Three thousand one hundred sixty-one PsA patients were included, with average age 58 ± 15.0 years, of whom 53.4% were women. Increased prevalence of DM-2, HLD, HTN, and obesity (OR 1.7, 1.5, 1.5, 1.5 respectively) was noted in the PsA group. Increased prevalence of IHD ($p < 0.0001$), PVD ($p < 0.0001$), CHF ($p = 0.002$), VHD ($p < 0.0001$), and cardiomyopathy ($p = 0.006$) was found in the PsA group compared to the control group even after adjusting for CVD risk factors.

Conclusions A high prevalence of CVD-related risk factors and morbidity was found in this Middle Eastern PsA population, in accordance with data from other geographic regions. These results emphasize the importance of clinician awareness of the increased risk for CVD-related complications in PsA patients.

Keywords Cardiovascular disease (CVD) risk factors · CVD-related morbidity · Psoriatic arthritis (PsA)

Introduction

Research has shown that psoriatic arthritis (PsA) patients have a higher prevalence of conventional cardiovascular disease (CVD) risk factors, including type 2 diabetes mellitus (DM-2), hyperlipidemia (HLD), obesity, and hypertension (HTN) [1–3], and an increased prevalence of CVD-related comorbidities, including ischemic heart disease (IHD), atherosclerosis, peripheral vascular disease (PVD), congestive heart failure (CHF), and cerebrovascular accident (CVA) [4–7]. Indeed, CVD was found to be the leading cause of death in the PsA patient population [5]. To date, several studies were published on the presence of CVD-related morbidity and mortality in PsA patients, but very few of these studies rely on actual population-based data, and to our knowledge, no large population studies currently exist on CVD-related morbidity in PsA patients in the Middle East. We therefore decided to evaluate

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for CVD-related risk factors and a wide range of CVD-related comorbidities in PsA patients using a large, Middle-East-based patient database.

Methods

A retrospective cross-sectional study was performed on data collected from the database of Israel's largest healthcare provider, Clalit Health Services (CHS), providing health services for 4.2 million people (comprising 52% of the Israeli population). The database receives input from pharmaceutical, medical, and administrative operating systems in real time. Patient diagnoses as reported by primary care physicians are modified to match the International Classification of Disease 9th Revision (ICD-9), which were found in a previous study to have high validity [8]. The database [9–11] was designed for purposes of administrative and clinical management and is available for use in epidemiological studies [8, 10, 11].

Study population

Data were collected on all patients with a diagnosis of PsA coded as "psoriatic arthropathy," "psoriasis with arthritis," or "arthritis, psoriatic" made by a rheumatologist or entered on hospital discharge summaries (all consistent with ICD-9 code 696.0). This patient cohort is described in detail in a previous study [10]. For each patient with PsA in the registry from 2000 to 2013, 10 age- and gender-matched control patients who had no history of psoriasis, rheumatoid arthritis, or ankylosing spondylitis were chosen as a control group from the same database.

Demographic data included age, sex, ethnicity (Jewish/Arab), and socioeconomic status at enrolment, the latter defined as low, medium, or high categories which correlate highly with the Israel Central Bureau of Statistics categories of SES status. CVD-related risk factors included current and past history of tobacco use, HLD, DM-2, HTN, and obesity. CVD-related morbidity included IHD (ischemic heart disease, angina pectoris, post coronary artery bypass status, post angiography, acute myocardial infarction, old myocardial infarction), valvular heart disease (VHD), congestive heart failure (CHF), cardiomyopathy, idiopathic hypertrophic subaortic stenosis (IHSS), cerebrovascular accident (CVA), carotid artery disease (CAD), peripheral vascular disease (PVD), and aortic aneurism.

The study was approved by the Carmel Hospital IRB. Requirement for individual patient consent forms was waived due to the retrospective, observational nature of the study.

Statistical analysis

Demographic and clinical characteristics were described in a descriptive analysis, with categorical variables presented as numbers and proportions. Chi-square test was used to compare categorical patient characteristics between PsA patients and controls. *t* test was used to compare the ages of the two groups, which were expressed as mean ± standard deviation (SD). Univariate and adjusted multivariate logistic regressions were employed to assess the relationship between CVD-related risk factors or CVD-related comorbidities and PsA. Valvular heart disease, IHSS, and cardiomyopathy, all of which have genetic, as well as CVD-related risk factors, were not included in the multivariate logistic regression model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. All data was analyzed using SPSS, version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). All tests were 2-sided; p values of < 0.05 were considered statistically significant.

Results

Our study included 3161 PsA patients and 31,610 age and sex-matched controls. The mean age of the entire cohort was 58 ± 15.0 years. Of the entire cohort, 16,870 (53.4%) were women. The ethnic distribution between Jewish 26,307 (83.2%) and Arab 5303 (16.8%) patients in the control group reflects the data from the Israeli Central Bureau of Statistics census of 2014 in which 20.7% of the Israeli population was of Arab ethnicity. The majority of the patients and the controls were of low and middle socioeconomic status (Table 1).

The following conventional cardiovascular risk factors were significantly more prevalent in the PsA patient group: obesity [OR = 1.71; CI (95%) 1.58–1.84, $p < 0.0001$], HLD [OR = 1.54; CI (95%) 1.43–1.67, $p < 0.0001$], HTN [OR = 1.51; CI (95%) = 1.40–1.62, $p < 0.0001$], and DM-2 [OR = 1.48; CI (95%) = 1.36–1.61 $p < 0.0001$]. Smoking was equally prevalent in the two groups: [OR = 1.05, CI (95%) = 0.97–1.14, $p = 0.259$] (Table 1). According to the univariate analyses, the following CVD-related morbidity was significantly more prevalent in the PsA group compared to the control group: cardiomyopathy [OR = 1.6; CI (95%) = 1.15–2.24, $p = 0.006$], PVD [OR = 1.47; CI (95%) = 1.24–1.75, $p < 0.0001$], IHD [OR = 1.39; CI (95%) = 1.27–1.53, $p < 0.0001$], VHD [OR = 1.36; CI (95%) = 1.17–1.57, $p < 0.0001$], CHF [OR = 1.29; CI (95%) = 1.1–1.5, $p = 0.002$], and CVA [OR = 1.17; CI (95%) = 1.03–1.34, $p = 0.02$]. There was no significant difference between the groups in the prevalence of carotid artery disease and IHSS.

After adjusting for age, sex, ethnicity, and CVD-related risk factors such as smoking status, HTN, HLD, and DM-2 in the multivariate analyses, IHD, PVD, CHF, and cardiomyopathy remained significantly more prevalent in the PsA patient group: cardiomyopathy [OR = 1.45; CI (95%) = 1.03–2.03, $p = 0.033$]; IHD [OR = 1.3; CI (95%) = 1.17–1.46,

Table 1 Description of the study population: psoriatic arthritis (PsA) and controls

		PsA patients $N = 3161$ No. (% of total)	Controls $N = 31,610$ No. (% of total)	p value	Odds ratio	CI (95%)
Age		58.36=/− 15.42	58.21 ± 15.99	$p = 0.605$		
Sex	Male	1474 (46.6%)	14,740 (46.6%)	$p = 1$		
	Female	1687 (53.4%)	16,870 (53.4%)			
Ethnicity	Jews	2801 (88.6%)	26,307 (83.2%)	$p < 0.0001$		
	Arabs	360 (11.4%)	5303 (16.8%)			
Socioeconomic status	Unknown	31(1%)	699 (2.2%)	$p < 0.0001$		
	Low	1012 (32%)	12,008 (38%)			
	Medium	1320 (41.8%)	12,436 (39.3%)			
	High	798 (25.2%)	6467 (20.5%)			
Tobacco use		904 (28.6%)	8742 (27.7%)	$p = 0.259$	1.05	0.97–1.14
Obesity		1091 (34.5%)	7464 (23.6%)	$p < 0.0001$	1.71	1.58–1.84
Diabetes mellitus		881(27.9%)	6545 (20.7%)	$p < 0.0001$	1.48	1.36–1.61
Hyperlipidemia		2022 (64%)	16,904 (53.5%)	$p < 0.0001$	1.54	1.43–1.67
Hypertension		1442 (45.6%)	11,313 (35.8%)	$p < 0.0001$	1.51	1.40–1.62

$p < 0.0001$]; PVD [OR = 1.28; CI (95%) = 1.06–1.53, $p = 0.009$]; and CHF [OR = 1.2; CI (95%) = 1.02–1.42, $p = 0.033$]. After adjusting for patient demographic differences and CVD-related risk factors, the relative increase in prevalence of CVA in PsA patients relative to the control group no longer remained statistically significant [OR = 1.05; CI (95%) = 0.91–1.21, $p = 0.494$] (Table 2). A comparative analysis among different epidemiological studies examining CVD-related disease and PsA is presented in Table 3.

Discussion

In our study, we found a higher prevalence of conventional CVD-related risk factors in our Middle East-based PsA patient population, which is in accordance with previous reports of higher prevalence of DM-2, HTN, dyslipidemia, and obesity in these patients [4–7]. Also, more prevalent were CVD-related comorbidities such as IHD, CHF, and PVD [1–3]. Our study is unique in documenting, for the first time, an increase in prevalence of cardiomyopathy and VHD in PsA patients.

Comparing our results with those of other investigators is complicated by differences in cohort size and study designs. While some studies were database-based analyses like ours [6, 7, 15], other studies were performed on smaller cohorts [12–14] using different comparators such as general healthy population [4, 7, 12, 14] versus other forms of arthritis [13]. In addition, studies were conducted in different geographic locations with different ethnic backgrounds such as American [6], Canadian [7, 14], Norwegian [15], Chinese [4, 13], and one small cohort of Israeli Jewish and Arab PsA patients [12]. Despite the demographic differences, most studies reported an increased risk for IHD in PsA patients (Table 3). The differences in the reported rate of IHD may be partially explained by inconsistency in the definition of the diseases (in some studies, it included history of angina pectoris and myocardial infarction [7], while in others, it included patients undergoing percutaneous coronary interventions [15], and yet, other studies like ours had a more general definition of coronary artery disease [14]. Our results are in line with Han et al. [6], while Mok et al. found an increased OR of 2.8 for IHD [13], and Gladman et al. [7] found a standardized prevalence ratio (SPR) of 2.57 for acute myocardial infarction.

Out of the three studies that assessed PVD, CVA, and CHF [6, 7, 15], only one [6] found a significantly increased risk for CVA. In our study, the relative increase in prevalence of CVA in PsA patients no longer remained statistically significant following adjustment for patient demographic differences and CVD-related risk factors. In two studies [6, 7], there was no significant increase in risk for CHF among PsA patients, which was not in accordance with our results. Our finding of a higher prevalence of PVD in PsA patients concurs with the OR of 1.5 for this comorbidity found by Han et al. [6], but not with the results of Gladman et al. where the prevalence of PVD was not significantly higher in PsA patients than controls [7].

In analyzing the prevalence of CVD-associated risk factors in the PsA population, we found that there was no significant difference in the relative prevalence of tobacco use among PsA patients and the control group in accordance with data from another Israeli study [12]. The report that smoking was more prevalent in the PsA patient population in the Norwegian PsA database [15] raises the question whether

Table 2 Cardiac comorbidities in PsA patients compared to the control group

	PsA patients no. (%) of total $N = 3161$	Controls no. (%) of total $N = 31,610$	Univariable model			Multivariate model*		
			Odds ratio	CI 95%	p value	Odds ratio	CI 95%	p value
Ischemic heart disease	601 (19%)	4561 (14.4%)	1.39	1.27–1.53	$p < 0.0001$	1.30	1.17–1.46	$p < 0.0001$
Peripheral vascular disease	155 (4.9%)	1070 (3.4%)	1.47	1.24–1.75	$p < 0.0001$	1.28	1.06–1.53	$p = 0.009$
Cerebrovascular accident	268 (8.5%)	2318 (7.3%)	1.17	1.03–1.34	$p = 0.019$	1.05	0.91–1.21	$p = 0.494$
Congestive heart failure	188 (5.9%)	1483 (4.7%)	1.29	1.1–1.50	$p = 0.002$	1.20	1.02–1.42	$p = 0.033$
Cardiomyopathy	40 (1.3%)	251 (0.8%)	1.60	1.15–2.24	$p = 0.006$			
Idiopathic hypertrophic subaortic stenosis	6 (0.2%)	47 (0.1%)	1.28	0.55–2.9	$p = 0.47$			
Carotid artery disease	6 (0.2%)	605 (1.9%)	1.33	1.05–1.68	$p = 0.17$	1.15	0.9–1.46	$p = 0.27$
Valvular heart disease	221 (7.0%)	1658 (5.2%)	1.36	1.17–1.57	$p < 0.0001$			

Logistic regression was performed separately for each item

*Adjusted for age, sex, smoking status, ethnicity, hypertension, hyperlipidemia, and diabetes mellitus

smoking is more prevalent in the PsA population in general or is influenced by other factors such as social habits and cultural norms.

Current studies agree that PsA patients tend to suffer from the metabolic syndrome, obesity in particular, in comparison to the general population. Indeed, metabolic syndrome seems to be more pronounced in the PsA patient population even more so than in other debilitating inflammatory arthritides including rheumatoid arthritis and ankylosing spondylitis [13]. The high worldwide prevalence of PsA despite different ethnic backgrounds and diets raises the question whether obesity is a cause or a consequence of PsA [16], or both. Accumulating data support the concept that obesity is a pro-inflammatory state caused by the endocrine and metabolic activity of the adipose tissue. Yet, this notion does not explain the relative increase in BMI in PsA patients relative to patients with other inflammatory diseases [3, 13, 17]. One possible explanation for the elevated body mass index (BMI) found particularly in PsA patients may stem from the psychological burden that psoriasis places on PsA patients, which may lead to avoidance of activities such as exercise. Indeed, the importance of psychologic factors affecting the health of patients with psoriasis and PsA is supported by the known tendency of PsA patients to suffer from depression, anxiety, and sleep disturbance [18]. Moreover, the skin and joint disease of PsA patients may constitute esthetic, as well as physical, barriers to the ability to perform physical activity [19–22].

It is noteworthy that psoriasis, even without co-existing PsA, was found to be related to higher prevalence of CVD-associated risk factors. Shapiro et al. [23] compared patients with psoriasis to those with other forms of dermatitis and found that psoriasis alone was associated with DM-2, HTN, obesity, and smoking. Using the Southern District Clalit Health Services (CHS) database, Cohen et al. [24] found a significantly increased prevalence of CVD-related risk factors in psoriasis patients. Similar to these studies, research highlighting the association between CVD-associated risk factors and psoriasis comes from Rodriguez-Zúñiga et al. [25], with work by Svedbom et al. [26] demonstrating increased mortality due to CVD-related comorbidities in patients with both mild and severe psoriasis.

When we assessed for the prevalence of other conventional CVD-related risk factors in PsA patients, we found that PsA patients had a higher prevalence of DM-2 and HTN, similar to previous studies, as well as significant dyslipidemia. Contrary to what one would expect, not all studies showed a statistically significant association between PsA and hyperlipidemia. One reason for this may be the use of different definitions for dyslipidemia, which also makes it difficult to compare results regarding the relative prevalence of dyslipidemia across studies. For instance, while some studies looked for high total cholesterol, high LDL, low HDL, and high triglycerides [1, 4, 13, 15], others looked for high total cholesterol and triglycerides [7] or for high total cholesterol alone [14]. Indeed, it remains unclear whether dyslipidemia is an independent CVD-related risk factor beyond the obesity phenomenon in the PsA patient population. Uniform measurements of these factors may help to evaluate their actual impact on cardiovascular disease in this population.

To the best of our knowledge, the increased prevalence of cardiomyopathy and VHD in PsA patients is reported here for the first time. Cardiomyopathy has a broad definition with multiple underlying etiologies depending on the type of cardiomyopathy, including genetic, acquired, infectious, autoimmune, or IHD-related. The most recent World Health Organization classification of cardiomyopathy has added inflammatory cardiomyopathy as a distinct entity, with idiopathic, autoimmune, and infectious forms [27]. The recognition of an autoimmune form of cardiomyopathy is of particular interest, given that preliminary investigations suggest that the frequency of autoimmune disorders, including psoriasis, was higher in first-degree relatives of the subjects with dilated

Table 3 Published epidemiological studies examining cardiovascular-related disease and PsA

Variable	1	2	3	4	5	6	7	8
Author	Han et al. [6] (2006)	Kimhi et al. [12] (2007)	Tam et al. [4] (2008)	Gladman et al. [7] (2009)	Mok et al. [13] (2011)	Khraishi et al. [14] (2014)	Gulati et al. [15] (2016)	Kibari et al. (present study)
Study Population	Cross-sectional database	Case control cross-sectional study	Case control cross-sectional study	Prospective cohort PsA mild–severe disease computerized database	Cohort from one hospital	Observational population-based cross-sectional study	population-based cohorts	Cross-sectional database
Number of patients	3066	47	102	648	109	196	323	3161
Country	USA	Israel	Hong Kong	Canada (Toronto)	China	Canada (Newfoundland)	Norway	Israel
Comparator	1:4 matched controls-patients in the database	100 healthy subjects	82 healthy subjects	Data from Canadian Community Health Survey	1. RA and AS patients 2. general population	2 cohorts: early PsA vs established PsA	50,468 participants of HUNT3 cohort	31,610 Non psoriasis non-inflammatory arthritis patients
DM-2	OR = 1.5		OR = 9.27		IFG = 2.58	13.8%		OR = 1.48
HTN	OR = 1.3		OR = 3.37	SPR = 1.9	No difference comparing to RA/AS	32.7%	OR = 1.39	OR = 1.51
Tobacco use					No difference compared to RA or AS			OR = 1.05
HLD	OR = 1.2				Low HDL OR = 2.8 when compared to RA / AS	61.6%		OR = 1.54
BMI						Obesity 59.7%		Obesity OR = 1.71
IHD	OR = 1.3			MI = 2.57 ANGINA = 1.97	OR = 2.8 compared to general population	8.7%		OR = 1.3
PVD	OR = 1.6							OR = 1.3
Carotid artery disease								OR = 1.14
CVA	OR = 1.3							OR = 1.05
CHF	OR = 1.5							OR = 1.2
VHD								OR = 1.36
CMP								OR = 1.45

DM-2 diabetes mellitus, *HTN* hypertension, *BMI* body mass index, *IHD* ischemic heart disease, *PVD* peripheral vascular disease, *CVA* cerebrovascular accident, *CHF* congestive heart failure, *HDL* high-density lipoprotein, *HLD* hyperlipidemia, *TG* triglycerides, *TC* total cholesterol, *MI* myocardial infarction, *IFG* impaired fasting glucose, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *AS* ankylosing spondylitis, *SPR* standardized prevalence ratio, *HUNT3* the Nord-Trøndelag Health Study data in 2006–2008

cardiomyopathy [27]. In the case of valvular heart disease, which also has diverse underlying etiologies depending on the type of valvular heart lesion, it is of particular interest that a recent study demonstrates increased frequency of mitral and tricuspid valve prolapse in patients with psoriasis [28].

Given the reported association between cardiomyopathy and certain valvular heart lesions with psoriasis, a limitation in our study is that information regarding the type, severity, and underlying etiology of cardiomyopathy and VHD were not available, so that an association between psoriatic arthritis and specific subtypes of cardiomyopathy or valvular heart lesions could not be assessed. In the case of VHD, mitral valve prolapse was not included in our analysis given that it has a different diagnostic code than that of valvular heart disease. Despite these limitations, our findings regarding a positive association between PsA and cardiomyopathy, as well as VHD, are of interest and demand further investigation, as PsA itself may be a risk factor for their occurrence and their presence may not be mere late sequela of atherosclerotic phenomena found in PsA patients.

Ongoing efforts to elucidate the factors contributing to the increase in CVD-related comorbidities in the PsA patient population are producing evidence that not all CVD-related morbidity is explained by the conventional CVD-related risk factors alone. While the underlying pathogenesis still remains unclear, it is thought to involve discrete and unique inflammatory and non-inflammatory factors stemming from the disease itself. Current evidence points to a complex mechanism involving systemic inflammation, insulin resistance, dyslipidemia, angiogenesis, oxidative stress, and endothelial dysfunction [29–31]. This concept is supported by evidence of endothelial dysfunction and early atherosclerosis found in PsA patients even with no classic CVD risk factors [32]. The report by Eder et al. [33] showing that intimal medial thickness and total plaque area are superior to the Framingham risk score for assessing CVD risk factors in PsA patients further strengthens the view that cardiovascular morbidity in these patients is not mediated solely by the traditional CVD risk factors [34]. It is of note that even current treatment for psoriatic arthritis does not seem to halt atherosclerosis progression [35].

Because of ongoing debate surrounding the relative magnitude of various CVD-related risk factors in PsA, CVD risk prediction and risk stratification in PsA patients have yet to be formally developed [36]. For example, Ernste et al. estimated CVD-associated risk in newly diagnosed PsA patients to be twofold greater than their Framingham risk score [37]. In a different study, Gulati et al. [15] evaluated the Systematic Coronary Risk Evaluation (SCORE algorithm), and showed that it underestimates the true CVD-related risk of PsA patients as it disregards the non-conventional CVD-associated risk factors such as elevated BMI, triglyceride level, and high sensitivity C-reactive protein which are known to be elevated in the PsA patient population. Indeed, the lack of agreement among investigators as to what constitutes CVD-associated risk factors in PsA patients and lack of a universally accepted multiplication factor for CVD risk in PsA patients using existing CVD risk calculators precluded our ability to estimate the precise CVD-associated risk of our PsA patient population in our study.

Additional limitations of our study include its cross-sectional design in which data were gathered from a computerized database at a single time point so that long-term patient follow-up on development of CVD-related risk factors over time was not possible, as well as the lack of data on PsA severity in the CHS database so that any association between PsA disease severity and the occurrence of CVD-related risk factors could not be assessed.

In conclusion, our study documents an increased prevalence of CVD-related risk factors in a large Mediterranean database and extends the spectrum of cardiac-related comorbidities to include cardiomyopathy and valvular lesions. Clinicians caring for PsA patients should be aware of the increased risk of CVD-associated morbidity in PsA patients, confirmed in different regions worldwide, and screen patients with PsA for CVD-related risk factors such as HTN, HLD, and DM-2. Further research is needed to explore new risk stratification methods for calculating CVD risk in PsA patients.

Compliance with ethical standards

Consent The study was carried out in compliance with the Helsinki Declaration. Internal Review Board approval was obtained from the Ethics Committee of Carmel Medical Center. Requirement for individual patient consent forms was waived due to the retrospective, observational nature of the study.

Disclosures None.

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