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INVESTIGATIVE REPORT

Psoriasis and Hypertension: A Case-Control Study

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In recent years, numerous reports have demonstrated an association between psoriasis and metabolic syndrome. However, some studies failed to demonstrate an association between psoriasis and hypertension. The aim of the present study was to examine the association between psoriasis and hypertension. Psoriasis patients of a health-maintenance organization were compared with enrollees without psoriasis regarding the prevalence of hypertension in a case-control study. The study included 12,502 psoriasis patients over the age of 20 years and 24,285 age- and sex-frequency-matched controls. The prevalence of hypertension was significantly higher in psoriasis patients than controls (38.8%, 29.1%, respectively, $p < 0.001$). In a multivariate analysis, hypertension was associated with psoriasis after controlling for age, sex, smoking status, obesity, diabetes, non-steroidal anti-inflammatory drugs (NSAIDs) and use of Cox-2 inhibitors (odds ratio: 1.37, 95% confidence interval: 1.29–1.46). The results of this study support the previously noted association between psoriasis and hypertension. We suggest that patients with psoriasis should be routinely screened for the presence of hypertension. ***Key words: hypertension; psoriasis; metabolic syndrome; chronic co-morbidity.***

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For decades it has been known that psoriasis is associated with smoking and obesity (1–4). Various disorders of plasma lipids, such as an increase in triglycerides and a decrease in high-density lipoprotein cholesterol have been shown in patients with psoriasis (5). In recent years, many reports have demonstrated an association between psoriasis and metabolic syndrome (1, 6–19), which is defined as a combination of central obesity, diabetes mellitus type 2 or insulin resistance, hypertension and dyslipidaemia (20–24). The association between psoriasis and metabolic syndrome is attributed to systemic inflammation, which occurs in patients with psoriasis, as well as in those with metabolic syndrome (25).

Surprisingly, even though hypertension is part of metabolic syndrome, several studies did not demonstrate an association between psoriasis and hypertension (4, 9, 11, 12), whereas other studies (10, 15, 16, 19) found a strong association between these two disorders, with odds ratios (OR) as high as 3 (19). The aim of the current study was to further assess the association between psoriasis and hypertension in a community-based approach, utilizing the large medical data-set of Clalit Health Services (CHS), Beer-Sheva, Israel.

MATERIALS AND METHODS

In the current study, data mining techniques utilizing the CHS database were used. CHS is the largest health provider organization in Israel, serving a population of approximately 3,800,000 enrollees. A comprehensive computerized database with continuous real-time input from pharmaceutical, medical and administrative computerized operating systems facilitates epidemiological studies such as the current analysis.

In recent years we have used the CHS database to study the association between psoriasis and metabolic syndrome (6, 7). The methodology of using the CHS database has been described previously (6, 7). Briefly, the CHS database was set up in 1997 and includes registration of 162 chronic conditions. Special field codes are used to describe the patients, who are defined as diagnosed with chronic diseases such as psoriasis or hypertension. Chronic disease registration and definitions were identical in cases and controls. The diagnoses are validated using multiple data sources in community medicine and hospital discharge records. Each diagnosis is confirmed by the primary physician. The validity of diagnoses in the register was previously estimated and found to be high for important chronic diagnoses (26). Additional data available from CHS database include age, sex, ethnicity (Jewish or Arab), geographical area of residence within Israel, and the socioeconomic status of patients. In order to minimize detection bias, the number of visits to the clinic was compared between cases and controls. Patients with psoriasis often have arthritis and could consume large amounts of non-steroidal anti-inflammatory drugs (NSAIDs) and cox-2 selective inhibitors. As these drugs could increase blood pressure, we also extracted data on use of these medications.

In the current study patients were defined as having psoriasis when there was at least one documented diagnosis of psoriasis in the medical records registered by a CHS physician in the community, or when psoriasis was listed in the diagnoses of the discharge letters from a hospital affiliated with CHS. The control group was randomly selected from the list of CHS members, excluding patients with a diagnosis of psoriasis, and was matched to controls regarding sex and age. Matching for age was performed within 10-year intervals.

The study was approved by the institutional review board of Soroka University Medical Center. Publication of the data was approved by the institutional committee of CHS general management.

The proportion of patients with hypertension was compared between patients with and without psoriasis by univariate analyses. Hypertension was identified when a diagnosis of

Table I. *Descriptive analysis of the demographic and clinical characteristics of case and control patients (n = 36,787)*

Characteristic	Psoriasis patients $n=12,502$	Controls $n=24,285$	p-value
Age (years), mean ± SD	55.8 ± 16.8	54.3 ± 17.5	<0.001
Median	56	55	
Range	20–101	20–110	
Male, % (*n*)	52.1 (6,516)	50.2 (12,197)	0.001
Socioeconomic status*, % (*n*)			
Low	32.6 (4,036)	38.2 (9,169)	<0.001
Medium	42.9 (5,308)	41.2 (9,892)	
High	24.5 (3,024)	20.6 (4,953)	
Hypertension, % (*n*)	38.8 (4,851)	29.1 (7,057)	<0.001
Smoking, % (*n*)	28.5 (3,558)	19.2 (4,669)	<0.001
Diabetes, % (*n*)	19.9 (2,484)	13.8 (3,352)	<0.001
Obesity, % (*n*)	24.5 (3,060)	15.6 (3,790)	<0.001
Ischaemic heart disease, % (*n*)	18.7 (2,340)	12.6 (3,058)	<0.001
Dyslipidaemia, % (*n*)	48.6 (6,078)	37.9 (9,215)	<0.001
NSAIDs, No. of prescription months			
Mean ± SD	4.5 ± 5.6	5.9 ± 6.2	<0.001
Median	3	4	
Any NSAIDs prescribed	87.1 (10,894)	78.2 (18,999)	<0.001
Cox-2 inhibitors, No. of prescription months			
Mean ± SD	0.9 ± 2.1	1.5 ± 2.9	<0.001
Median	0	0	
Any NSAIDs prescribed	45.6 (5,699)	33.7 (8,183)	<0.001

SD: standard deviation; NSAIDs: non-steroidal anti-inflammatory drugs.
*Socioeconomic status was missing for 134 patients with psoriasis and 271 controls.

hypertension was made in a primary care visit or when blood pressure levels were repeatedly higher than 140/80 mmHg. The diagnosis of hypertension was verified by the primary care physician within the database. Chi-square tests were used to compare categorical parameters between the groups and *t*-tests for comparison of continuous variables. Logistic regression models were used to measure the association between psoriasis and hypertension in a multivariate analysis. Statistical analysis was performed using SPSS software, version 13.

RESULTS

The study included 12,502 psoriasis patients over the age of 20 years and 24,285 age- and sex-matched controls. The case group was 1.5 years older and had a higher proportion of males compared with the control group. Descriptive analyses of the demographic characteristics of case and control patients appear in Table I.

The prevalence of hypertension was significantly greater in psoriasis patients compared with the control group (38.8%, 29.1%, respectively, $p<0.001$). When adjusted for age and sex, the association between psoriasis and hypertension appears to be significant only above the age of 40 years (data not shown).

The distribution and OR of risk factors for hypertension by sex in patients with psoriasis compared with the control group are described in Table II. In a multivariate analysis, hypertension was associated with psoriasis, after controlling for age, sex, smoking status, obesity, diabetes, NSAIDS and Cox-2 inhibitors use OR 1.37, 95% confidence interval (95% CI) 1.29–1.46; Table III).

DISCUSSION

In the current population-based study we observed an association between psoriasis and hypertension, which may be attributed to angiotensin II, a product of angiotensin-converting enzyme (ACE) that regulates vascular tone and stimulates the release of pro-inflammatory cytokines (27). Elevated plasma renin activity has been reported in patients with psoriasis (28–30). The association between psoriasis and hypertension may also be attributed to the production of endothelin-1, which is produced by keratinocytes as an autocrine growth factor. Bonifati et al. (31) reported that endothelin-1 was increased in both sera and lesional skin of patients with psoriasis, compared with controls. Endothelin-1 levels were correlated with psoriasis severity (31). Endothelin-1 is a potent vasoconstrictor and may contribute to hypertension in psoriasis patients. Oxidative stress, which is present in patients with psoriasis, may play a role in hypertension by destructive effects of reactive oxygen species, damaging endothelium-dependent vasodilatation (32). Patients with psoriasis often have

Table II. *Risk factors for hypertension in patients with psoriasis compared with the control group*

	Females			Males		
	Psoriasis patients ($n=5986$) % (*n*)	Control group ($n=12,088$) % (*n*)	OR for hypertension (95% CI)	Psoriasis patients ($n=6516$) % (*n*)	Control group ($n=12\,197$) % (*n*)	OR for hypertension (95% CI)
Age (years, mean ± SD)	55.8 ± 16.4	54.9 ± 17.9	NA	55.8 ± 16.4	53.8 ± 17.0	NA
Socioeconomic status*						
Low	31.8 (1,884)	37.3 (4,460)	1.0	33.4 (2,152)	39.1 (4,709)	1.0
Medium	43.7 (2,592)	41.4 (4,946)	1.2 (1.1–1.3)	42.2 (2,716)	41.0 (4,948)	1.2 (1.1–1.3)
High	24.5 (1,451)	21.4 (2,555)	1.3 (1.2–1.5)	24.4 (1,573)	19.9 (2,398)	1.4 (1.3–1.5)
Smoking	21.0 (1,256)	12.2 (1,471)	1.9 (1.8–2.1)	35.3 (2,302)	26.2 (3,198)	1.5 (1.4–1.6)
Obesity	28.4 (1,701)	17.7 (2,138)	1.8 (1.7–2.0)	20.9 (1,359)	13.5 (1,652)	1.7 (1.5–1.8)
Diabetes	19.8 (1,183)	13.2 (1,600)	1.6 (1.5–1.7)	20.0 (1,301)	14.4 (1,752)	1.5 (1.4–1.6)

SD: standard deviation; OR: odds ratio; CI: confidence interval; NA: not applicable.
*Data was missing for 405 patients, evenly distributed across study groups and sex.

Table III. *Factors associated with hypertension (logistic regression model) (n = 36,787)*

Risk factor	OR for hypertension (95% CI)
Psoriasis (vs. controls)	1.37 (1.29–1.46)
Male sex (vs. female)	1.03 (0.96–1.09)
Age (per 5 year increment)	1.57 (1.55–1.59)
Smoking (yes vs. no)	1.24 (1.15–1.32)
Obesity (yes vs. no)	3.45 (3.25–3.68)
Diabetes (yes vs. no)	2.95 (2.75–3.17)
Number of visits (per additional 5 visits)	1.04 (1,03–1.05)
Ever prescribed NSAIDs (vs. never)	1.47 (1.34–1.61)
Ever prescribed Cox-2 inhibitors (vs. never)	1.17 (1.10–1.24)

CI: confidence interval; OR: odds ratio; NSAIDs: non-steroidal anti-inflammatory drugs.

arthritis, which is treated with medications such as NSAIDs and Cox-2 inhibitors. These medications could also contribute to increased blood pressure. However, in the present study, the association between psoriasis and hypertension persisted after controlling for use of NSAIDs and Cox-2 inhibitors.

A literature search revealed 9 publications relating to the association between psoriasis and hypertension (Table IV). Only 4 of these (44%) supported the association.

It is possible that some of these studies had overestimated the association between psoriasis and hypertension due to a Berksonian bias, whereas other studies might have underestimated the association due to over-matching. In the following paragraphs we discuss these divergences.

Several studies included hospitalized patients with psoriasis and either compared them with ambulatory controls, or compared the proportion of hypertension in these patients with estimates from the general population. A strong association was reported in these studies, with an OR as high as 3. This possible methodological limitation was first described in 1946 by Berkson (33), and is named "Berksonian bias". Berksonian bias is a spurious association between a disease and a factor suspected to be associated with the disease because of the different probabilities of admission to a hospital for those with the disease, without the disease and with the associated factor of interest. It is possible that patients with psoriasis and metabolic syndrome are more likely to be hospitalized because of their co-morbidities. Therefore, the strong association between psoriasis and hypertension may reflect, in part, the fact that patients with psoriasis and metabolic syndrome components are more frequently admitted to hospitals. In the current study, we eliminated Berksonian bias by using a community-based database.

A few of the studies we have reviewed used controls who had dermatological problems other than psoriasis. These studies generally did not find an association between psoriasis and hypertension. It is possible that some over-matching has occurred in these studies, e.g. controls with inflammatory skin disease may also have an association with metabolic syndrome. To avoid both a Berksonian-type bias as well as over-matching, investigators should strive to select hospitalized controls when the cases are hospitalized patients and to reduce the chance of the controls having elevated levels of the risk factor due to the selection criteria, in this case, controls with non-inflammatory dermatoses or skin neoplasm. Overmatching was also avoided in the current study, in which controls were patients in primary care, rather than dermatology patients.

Another possible limitation in some previous studies is the use of a young cohort of patients with psoriasis. In the current study, the association between psoriasis and hypertension was statistically significant in the age-specific analyses among females over the age of 40 years and among males over the age of 30 years. Possible explanations are that this association is valid only in older patients, or that considering the low prevalence of hypertension in young subjects, most studies may have limited size and power to detect a statistically significant association.

Table IV. *Literature search on the association between psoriasis and hypertension*

Author	Country	Patients *n*	Controls *n*	Patients, age (mean years)	Proportion of hypertension		Significance	Observed/ expected ratio	Adjusted odds ratio
					Patients	Controls			
Cohen et al., 2008 (present case)	Israel	12,502	24,285	55.8	38.8%	29.1%	Yes		1.37
Gisondi et al., 2007 (9)	Italy	338	334	62.1	NS	NS	No		
Henseler & Christophers, 1995 (10)	Germany	2,941	39,520	NS	11.4%	NS	Yes	1.9	
Huerta et al., 2007 (11)	UK	3,994	10,000	NS	NS	NS	No		
Inerot et al., 2005 (12)	Sweden	570	647	40.2	NS	NS	No		
Lindegard 1986 (14)	Sweden	372	159,200	NS	NS	NS	Yes	3–6	
Naldi et al., 2001 (4)	Italy	560	690	NS	8.9%	8.8%	No		
Neimann et al., 2006 (16)	UK	127,706[a]	465,252	46.4	14.7%	11.9%	Yes		1.03–1.16
		3,854[b]	465,252	49.8	20.0%	11.9%	Yes		1.00–1.25
Pearce et al., 2005 (17)	USA	753	US pop	55	28.7%	20.3%	N.S.		
Sommer et al., 2006 (19)	Germany	625	1,044	54.4 (median)	21.9%	10.2%	Yes		3.27

[a]Mild psoriasis; [b]Severe psoriasis.
NS: not stated.

The main limitation in our study is the lack of clinical validation of psoriasis; this limitation appears also in other studies that were reviewed (Table IV). Due to the large sample size, the infrastructure of the CHS database and regulative limitations, it is impossible to validate each case. Therefore, misclassification (differential or non-differential) cannot be completely ruled out in the current study.

In summary, our observation supports previous reports of an association between psoriasis and hypertension, which is biologically plausible. Additional studies are needed to further confirm this association, while taking all possible measures to avoid biases such as the Berksonian bias or over-matching. In addition, we suggest that patients with psoriasis should be routinely screened for the presence of hypertension.

The authors declare no conflict of interest.

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