

## Original Article

# Linking the PASI of sufferers from moderate and severe psoriasis to an increase of carotid intima-media thickness: a cross-sectional study

## 中重度銀屑病患者的銀屑病皮損面積和嚴重度指數(PASI)與頸動脈內膜中層厚度增加的相關聯橫斷面研究

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Psoriasis is a multisystemic disease which has been related with comorbidities such as metabolic syndrome and arteriosclerosis through a psoriasis-related inflammatory chronic state. In order to assess the relationship of psoriasis with carotid intima-media thickness (IMT), 100 moderate-to-severe psoriatic patients were studied. Increased PASI score was associated with a higher IMT. Additionally, a higher IMT was observed with the increasing of erythrocyte sedimentation rate. In conclusion, patients with moderate-to-severe psoriasis are at higher risk of an increased IMT.

銀屑病是一種多系統的疾病，因其慢性的炎症性狀態，已發現相關的合併症包括代謝綜合徵和動脈硬化。為了評估銀屑病與頸動脈內膜中層厚度（IMT）的關係，我們對100名中度至重度銀屑病患者進行了研究，發現銀屑病皮損面積和嚴重度指數評分高者相應地頸動脈內膜中層厚度較厚。此外，頸動脈內膜中層厚度較厚者亦觀察到有紅細胞沉降率升高。總括來說，中重度銀屑病患者有著較高的頸動脈內膜中層增厚風險。

**Keywords:** Atherosclerosis; chronic inflammation; intima-media thickness; psoriasis; TNF-alpha

關鍵詞：動脈粥樣硬化、慢性炎症、內膜中層厚度、銀屑病、甲型腫瘤壞死因子

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## Introduction

Psoriasis is a chronic, inflammatory and multisystem condition with a prevalence which ranges from the 0.91% to the 8.5% of global population.<sup>1</sup> The systemic inflammatory state of psoriasis is associated with increased risk of hypertension, hyperlipidaemia, metabolic syndrome and arteriosclerosis,<sup>2,3</sup> and has become a matter of interest in recent years. The risk of developing major adverse cardiac events (MACEs) in these patients is also increased.<sup>4</sup>

The development of arteriosclerosis is considered to be a key feature of MACEs, such as ischaemic ictus or myocardial infarction.<sup>5</sup> A wide range of cell types (e.g., endothelial cells, smooth muscle cells, immune cells and haematopoietic progenitors) are involved during the atherogenic process, in which the development of reactive species of oxygen and nitrogen plays a fundamental role.<sup>6,7</sup> Moreover, the endothelial inflammation leads to monocyte recruitment during CCR5 and CC2 expressions on the surface of endothelial cells.<sup>8</sup> This process, usually linked to the accumulation of cholesterol and smooth muscle cells in the intima, is accompanied by the transformation of monocytes into foam cells. As a result, lipids are deposited in the arterial wall.<sup>9,10</sup>

Due to the major inflammatory component present in both entities, several studies have indicated that psoriasis patients are more likely to suffer from arteriosclerosis. Following this assumption, it must be stated that there is evidence that some of the cytokines associated with psoriasis-related injuries (TNF- $\alpha$ , IL-17, IL-23) are also present in the chemotaxis process in which monocytes move towards the arterial wall during the growth of the arteriosclerotic plaque.<sup>11,12</sup>

Following the advice given by the European Society of Cardiology,<sup>13</sup> medical imaging to detect cardiovascular illness in high risk patients is being increasingly used. Several studies have therefore

shown that increased carotid intima-media thickness (IMT) – measured with carotid ultrasound – in the common carotid artery could be tightly linked to a higher risk of coronary artery pathology, particularly given that IMT is considered to be an indicator of generalised arteriosclerosis.<sup>14-16</sup> A large number of studies have since focused on confirming the presence of a raised IMT in psoriatic patients.<sup>15,17,18</sup> Some of these authors have linked this incremented IMT with the Psoriasis Area Severity Index (PASI) and with inflammatory markers such as C-Reactive Protein (CRP).<sup>19</sup>

In view of these findings, the present study evaluated the relationship between moderate and severe psoriasis and IMT. Our study is adjusted to accommodate for confounding factors related to metabolic syndrome and to pro-inflammatory markers. The aim of this research is to analyse the relationship between psoriasis and the risk of developing arteriosclerosis taking into account that both pathologies may alter the patients' systemic state.

## Method

### Patients

A total of 100 patients with moderate and severe psoriasis were recruited and monitored in the Psoriasis Unit of our hospital. Inclusion criteria were as follows: a) age 18 or over 18; b) PASI greater than or equal to 5; c) patients had to be resident in the metropolitan area of Granada. Exclusion criteria were as follows: a) previous use of systemic or biological drugs for treating psoriasis; b) presence of atheromatous plaque during the ultrasound; c) antecedents of rheumatoid arthritis; d) inflammatory bowel disease; e) angina pectoris or myocardial infarction; f) ictus and intermittent claudication, and g) presence of chronic renal or hepatic illness detected through analytical parameters. Their data were compared with 65 healthy controls from the same area. Every patient agreed with the terms present in the WMA Declaration of Helsinki

and the investigation was approved by the Ethical Committee of the Hospital Universitario Virgen de las Nieves (Granada, Spain).

### **Clinical parameters and questionnaires**

The age and sex of every patient were documented in the study. Each patient filled the questionnaires Psoriasis Epidemiology Screening Tool (PEST),<sup>20</sup> Psoriasis Arthritis Screening Evaluation (PASE)<sup>21</sup> and Early Arthritis for Psoriatic Patients (EARP),<sup>22</sup> as a means of screening psoriatic arthritis. The presence of this type of arthritis was considered if two out of the three questionnaires exhibited positive results (PEST greater than or equal to 3; PASE greater than or equal to 44; EARP greater than or equal to 3). Furthermore, the patients were surveyed on their tobacco use. Measurement of PASI was also undertaken, while each patient's body mass index (BMI) was calculated. Blood pressure was measured at three different times within two consecutive weeks to rule out the presence of arterial hypertension (HTN).

### **Analytical measurements**

Blood tests were performed after twelve hours fasting. The following parameters were measured: the lipid parameters low-density lipoprotein (LDL) and triglycerides (TG); hepatic metabolite alanine aminotransferase (ALT); glycaemia and glycated haemoglobin (Hb1ac); the pro-inflammatory markers erythrocyte sedimentation rate (ESR) and C Reactive Protein (CRP), and vitamin D levels.

### **Measurement of carotid IMT**

The left common carotid artery was assessed as follows: patients were placed in a supine position with their necks being 60° laterally inclined. Six measurements of IMT were performed with the sounding line being 10mm away from the carotid bifurcation. Only measurements with a standard deviation of less than 20 micrometres were taken into consideration. A high-res ultrasound scanner (Esaote MyLab Gold 25) with a 10 MHz sounding line running specific software for measuring IMT (Esaote QIMT Software)

was employed. The definitive value of the IMT measurements was obtained by calculating the average of the six valid measurements from the sound scanning.

### **Statistical methods**

A descriptive analysis was performed, aiming to define the general characteristics of the patients in this study. Binary logistic regression analysis of the hypothetical associations between these variables was performed. This test was first conducted with a raw, unprocessed model and then with one adjusted to the variables here at study. The response variable was the presence of a higher-than-average IMT in the left carotid ( $p < 0.05$ ). This analysis was conducted to construct a new model that could be distributed in relation to the patients' sex. The software SPSS 22.0 (IBM Corp, Armonk, NY) was used for data analysis.

### **Results**

The demographics of the patients are shown in Table 1. The mean age of the patients was 46.9 years old of which 54% were males. Furthermore, the BMI of the patients presented with class I obesity. Moreover, the mean IMT of the psoriatic patients was  $632.43 \pm 122.60$   $\mu$ metres, which was significantly higher than the mean IMT of the control group ( $p = 0.015$ ). The logistic regression analysis of the left-carotid IMT indicated that patients with increased PASI (OR 1.458; CI 95% 1.052-2.202;  $p = 0.024$ ) were more likely to present a greater-than-average IMT (Table 2). Correlation model between PASI and IMT showed a positive correlation between IMT and PASI that reached statistical significance ( $r = 0.201$ ;  $p = 0.042$ ) and demonstrated that the increase in PASI levels was associated with an increased IMT (Figure 1). The increase in risk was also connected to a raised ESR (OR 1.205; CI 95% 1.032-1.407;  $p = 0.019$ ). A high IMT was linked to the presence of arterial HTN

and to an increase of the hepatic parameter ALT. None of the other variables correlated to the left carotid IMT thickness. Males were more likely to have a raised IMT with a raised PASI (OR 1.518; CI 95% 1.008-2.284,  $p=0.048$ ) and ALT (Table 3). In women, this same analysis showed that an increased PASI was more likely to present an elevated IMT. Nonetheless, these results did not reach statistical significance ( $p=0.096$ ) in female patients.

## Discussion

After being adjusted in order to avoid confounding factors, the present study has shown an increased

risk of IMT in patients suffering from psoriasis who also present with a high PASI and ESR. Moreover, it has been observed how an increased IMT is related to the presence of HTN and to an increased ALT.

Although not directly connected to the main aim of this study, some of the results are worth noting. First of all, it must be stated that the 54% percent of the studied patients were males – consequently, the female patients represented the 46% percent of our study subjects. According to recent research performed on American,<sup>23</sup> and Spanish populations,<sup>24</sup> this ratio is in line with the distribution of psoriasis in Caucasian patients. Another point to note is that our psoriatic patients presented a high BMI, falling under the Obesity I

**Table 1.** Clinical characteristics of the study patients

	Psoriasis (Mean/N)	Control (Mean/N)	p
Age	46.90+/-14.52	49.57+/-10.85	0.315
Sex			0.567
M	54	35	
F	46	30	
PASI	7.55+/-5.21	NA	NA
PsA		NA	NA
Yes	33		
No	67		
BMI (kg/m <sup>2</sup> )	30.06+/-6.50	25.88+/-3.21	<b>&lt;0.001</b>
Smoking			0.242
Yes	36	20	
No	64	45	
Hypertension			0.165
Yes	29	15	
No	71	50	
IMT (micrometres)	632.43+/-122.60	585.22+/-110.40	<b>0.015</b>
ESR (sec)	11.09+/-9.05	5.48+/-3.44	<b>&lt;0.001</b>
CRP (mg/dL)	1.18+/-2.72	0.51+/-0.94	<b>&lt;0.001</b>
Triglycerides (mg/dL)	145.85+/-127.65	129.44+/-116.73	0.198
LDL (mg/dL)	118.13+/-30.50	110.24+/-26.68	0.386
ALT (IU/L)	26.41+/-17.21	22.63+/-14.78	0.401
Glycaemia (mg/dL)	105.74+/-45.15	90.83+/-32.21	<b>&lt;0.001</b>
hB1ac (%)	5.87+/-1.19	4.24+/-0.97	0.072
Vitamin D (ng/dL)	20.86+/-8.65	28.54+/-7.29	<b>&lt;0.001</b>

PASI: Psoriasis Area Severity Index; PsA: Psoriatic arthritis; BMI: Body mass index; IMT: Intima-media thickness; ESR: Erythrocyte Sedimental Rate; CRP: C Reactive Protein; LDL:Low-density lipoprotein; ALT: Alanine aminotransferase; hB1ac: Glycosylated haemoglobin.

Class. Several studies performed before the present one have displayed a noticeable link between psoriasis and the BMI. Therefore, a positive correlation between the BMI and the risk of developing psoriasis can be traced.<sup>25,26</sup>

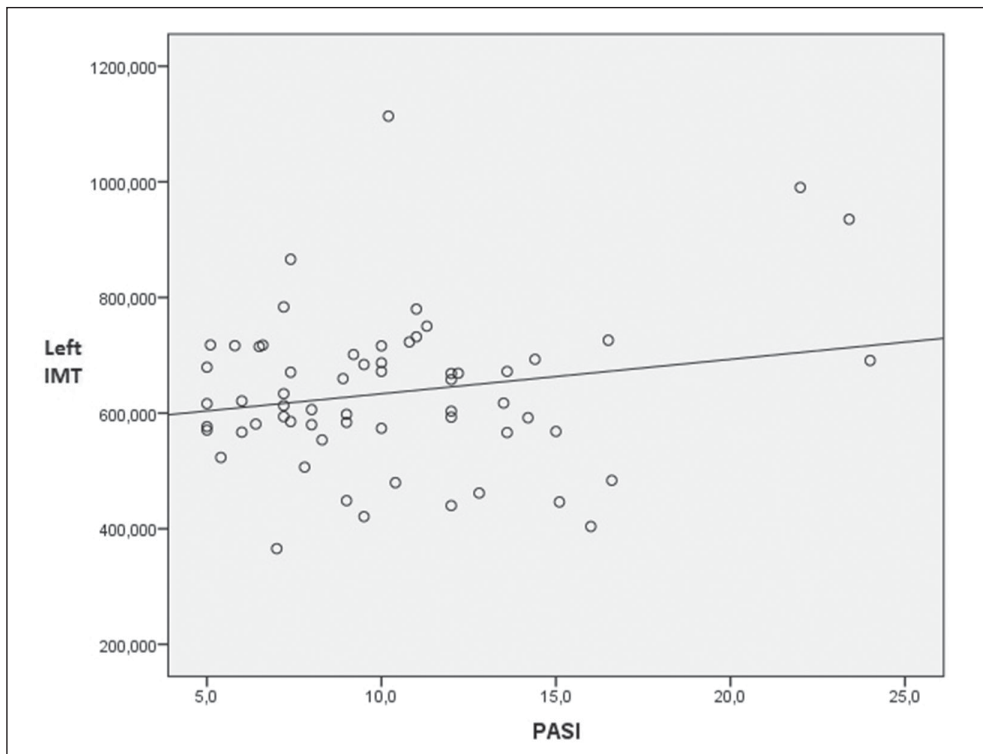
The results obtained in this study are in line with previous research on the relationship between an increased IMT and psoriasis. In 2007, Kimhi et al found that patients suffering from psoriatic arthritis presented a larger IMT than patients who did not suffer from this condition and that they had an increase in CRP.<sup>27</sup> Back in 2009, Baldi et al considered the presence of a increased IMT in patients with plaque psoriasis, although they did not identify a correlation between PASI levels and the IMT.<sup>28</sup>

When considering carotid intima-media thickness, previous studies have noted the association with hypertension in psoriatic patients. This has been seen in longitudinal studies,<sup>29</sup> as well as in case-control studies.<sup>30</sup> For instance, El-Mongy et al observed in their case-control study that psoriatic patients presented an abnormal IMT and that there was a positive correlation with the patients' age, PASI and arterial hypertension.<sup>31</sup> Similar results were obtained by Karoli et al after performing a multivariate analysis conducted in a cross section study of Indian population.<sup>32</sup> The above results are in line with ours, which have shown that psoriatic patients with arterial hypertension are more likely to present with an increased IMT. Furthermore, the present study has shown the connection between a raised ALT and increased IMT. A number of studies

**Table 2.** Multivariate analysis for left intima-media thickness

	Crude model				Adjusted model			
	OR	CI(95%)		p	OR	CI(95%)		p
Age	1.051	1.018	1.085	<b>0.002</b>	1.083	0.975	1.203	0.135
Sex	0.818	0.371	1.805	0.620	2.199	0.273	17.693	0.459
PASI	1.047	0.969	1.133	0.244	<b>1.459</b>	1.052	2.022	<b>0.024</b>
PsA	0.923	0.373	2.987	0.863	3.333	0.307	36.167	0.322
HBP	0.442	0.179	1.092	0.077	<b>4.755</b>	1.125	14.831	<b>0.048</b>
BMI	1.017	0.955	1.082	0.603	0.882	0.737	1.056	0.172
Smoking	0.727	0.319	1.656	0.448	6.371	0.536	75.560	0.142
ESR	1.015	0.966	1.066	0.584	<b>1.205</b>	1.032	1.407	<b>0.019</b>
CRP	0.817	0.626	1.105	0.614	0.988	0.955	1.022	0.478
TG	1.003	0.998	1.007	0.216	1.014	0.996	1.032	0.137
LDL	1.006	0.992	1.020	0.402	1.024	0.993	1.055	0.134
ALT	1.029	0.999	1.060	0.057	<b>1.122</b>	1.009	1.247	<b>0.033</b>
Glycaemia	1.008	0.997	1.018	0.153	1.035	0.980	1.092	0.216
hB1ac	1.386	0.910	2.212	0.128	0.436	0.176	1.798	0.251
Vitamin D	0.996	0.947	1.047	0.885	0.986	0.846	1.148	0.853

PASI: Psoriasis Area Severity Index; PsA: Psoriatic arthritis; HBP: High blood pressure; BMI: Body mass index; ESR: Erythrocyte Sedimental Rate; CRP: C Reactive Protein; TG: Triglycerides; LDL:Low-density lipoprotein; ALT: Alanine aminotransferase; hB1ac: Glycosylated haemoglobin; OR: Odds Ratio; CI: confidence interval



**Figure 1.** Correlation between Psoriasis Area Severity Index and left intima-media thickness ( $r=0.201$ ).

**Table 3.** Multivariate analysis for left intima-media thickness stratified by sex

	Male			Female				
	OR	CI(95%)	p	OR	CI(95%)	p		
Age	1.117	0.972	1.278	0.191	1.127	0.963	1.318	0.136
PASI	<b>1.518</b>	1.008	2.284	<b>0.046</b>	1.107	0.993	1.453	0.096
PsA	0.845	0.554	2.121	0.754	0.510	0.028	9.465	0.652
HBP	0.572	0.121	6.206	0.414	0.946	0.036	24.548	0.974
BMI	0.955	0.761	1.309	0.352	0.959	0.793	1.160	0.669
Smoking	0.238	0.005	11.443	0.468	0.263	0.010	6.674	0.418
ESR	1.024	0.959	1.279	0.245	1.049	0.900	1.223	0.348
CRP	0.714	0.522	1.324	0.644	0.655	0.124	4.256	0.547
TG	1.105	0.889	1.845	0.414	1.004	0.876	1.845	0.451
LDL	1.010	0.963	1.060	0.678	1.077	0.996	1.157	0.074
ALT	<b>1.131</b>	1.001	1.279	<b>0.048</b>	0.915	0.760	1.027	0.338
Glycaemia	1.070	0.969	1.182	0.179	0.999	0.973	1.027	0.967
hB1ac	0.940	0.755	2.212	0.567	0.924	0.645	3.187	0.502
Vitamin D	0.841	0.649	1.191	0.341	0.755	0.437	2.231	0.408

PASI: Psoriasis Area Severity Index; PsA: Psoriatic arthritis; HBP: High blood pressure; BMI: Body mass index; ESR: Erythrocyte Sedimental Rate; CRP: C Reactive Protein; TG: Triglycerides; LDL: Low-density lipoprotein; ALT: Alanine aminotransferase; hB1ac: Glycosylated haemoglobin; OR: Odds Ratio; CI: confidence interval



have indicated the correlation between fatty liver and endothelial dysfunction and the appearance of elevated transaminases.<sup>33,34</sup> A recent study performed on an obese paediatric population has shown that ALT and TNF-alpha are independent factors to be taken into account when studying ILT levels.<sup>35</sup> These results confirm the relevance that chronic inflammation is related to subclinical arteriosclerosis.

According to clinical studies, psoriasis medications such as methotrexate or anti-TNF agents have been associated with a decrease in cardiovascular events in psoriatic patients. Moreover, other preliminary studies on psoriatic patients have demonstrated that methotrexate,<sup>36</sup> or anti-TNF agents,<sup>37</sup> may lead to a diminished IMT. Nevertheless, it must be stated that the connection between these treatments and the decrease of IMT levels has not been sufficiently established. Indeed, there are several studies that have reported progression of IMT in psoriasis patients treated with these agents.<sup>38</sup>

There are a number of limitations with our study. For instance, there is a lack of follow-up and of the presence of a control group. It must also be noted that, while a number of studies highlight the association between psoriasis and the risk subclinical arteriosclerosis and MACEs,<sup>18,39</sup> this has not been seen in other studies.<sup>40</sup>

In conclusion, the present study has indicated a relationship between psoriasis and carotid IMT as measured by the chronic inflammatory mechanism in psoriatic patients. Our results highlight the need for adequate primary prevention of subclinical arteriosclerosis in psoriatic patients. Furthermore, we believe that there should be greater emphasis on the early detection of subclinical arteriosclerosis to avoid MACEs. Finally, further research into how the various systemic and biological treatments of psoriasis can lead to possible reversibility of subclinical arteriosclerosis is needed.

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