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# Predictive factors for the development of diabetes in Psoriatic Arthritis

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***Abstract:*** ***Introduction****: Psoriatic arthritis (PsA), a chronic inflammatory rheumatic disease, affects both genders, leading to joint symptoms, skin manifestations, and various concurrent medical conditions. Diabetes is a prevalent and variable comorbidity in PsA, with inflammatory mechanisms contributing to cardiovascular diseases, highlighting the need for systematic screening and management of comorbidities in PsA. The objective of our study focuses on assessing the prevalence of diabetes in PsA and identifying associated factors.* ***Materials and Methods:*** *This study is retrospective in nature, focusing on a cohort of individuals diagnosed with psoriatic arthritis based on the Classification Criteria for Psoriatic Arthritis (CASPAR) from the year 2006.These individuals were followed and managed between January 2011 and February 2023. Clinical, biological, and radiographic data were collected.* ***Results:*** *Our study encompassed a cohort of 99 individuals diagnosed with PsA. The average age of these patients was 55.16 years, with a standard deviation of ±14.9 years. The male-to-female sex ratio was 0.41. The average disease duration was 7.56 years +/- 8.8. Diabetes was present in 17.2% of the patients. Our study finds that diabetes was more common in patients who had hypertension (p=0.003), patients with dyslipidemia (p=0.002), those with a personal history of cutaneous psoriasis (p=0.03), patients with a total hip replacement (PTH) (p=0.04), and menopausal patients (p=0.004). Additionally, the mean vitamin D levels were higher in diabetic patients compared to the non-diabetic group. This difference is statistically significant with p=0.04.Hypertension (HTA) and anti-citrullinated protein antibodies (ACPA) were significantly associated with diabetes in the context of PsA.* ***Conclusion:*** *our study identified HTA, ACPA, dyslipidemia, menopause, and a personal history of cutaneous psoriasis as predictive factors for the development of diabetes in PsA.*

**Keywords:** diabetes, psoriatic arthritis, comorbidity.

## Introduction:

Psoriatic arthritis (PsA) is a persistent inflammatory rheumatic condition categorized under spondyloarthritis. It impacts individuals of both genders, manifesting with diverse joint symptoms, skin manifestations, and frequent coexisting medical conditions that collectively contribute to a decline in quality of life and an escalation in morbidity and mortality. The etiopathogenesis of PsA is intricate and not fully comprehended. The prevailing hypothesis proposes an intricate interplay between genetic predisposition factors, primarily HLA B27, and environmental triggers such as mechanical stress, trauma, infection, and smoking in individuals with psoriasis. This interaction results in the dysregulation of immune-inflammatory pathways [1-2].
Diabetes stands out as one of the most prevalent comorbidities in PsA, exhibiting variable frequencies and degrees of severity.

Beyond the well-known inflammatory mechanisms in the development of cardiovascular diseases during chronic inflammatory rheumatism, adipose tissue and adipokine production play a crucial role. Anxiety, depression, and fibromyalgia are also major comorbidities to be considered.
The elevated occurrence of metabolic syndrome in individuals with psoriatic arthritis emphasizes the imperative for systematic screening, assessment, and vigilant monitoring of diabetes mellitus, obesity, hypertension, and dyslipidemia in patients with psoriasis.
Screening and management of other comorbidities common to chronic inflammatory rheumatism (cancers, infections) have been the subject of recommendations and are now part of best practices. Systematic screening and recommendations from professional societies are necessary and beneficial but raise questions about practical applicability and medical inertia. The involvement of therapeutic education nurses and the development of advanced practice nurses are significant challenges to improve the prevention and overall management of patients with chronic diseases.
This study aims to ascertain the prevalence of diabetes in Psoriatic Arthritis and identify the factors associated with its occurrence.

## Materials and Methods:

This study is retrospective in nature, focusing on a cohort of individuals diagnosed with psoriatic arthritis based on the Classification Criteria for Psoriatic Arthritis (CASPAR) from the year 2006.These individuals were followed and managed at the Hassan 2 University Hospital in Fes between January 2011 and February 2023. Clinical, biological, and radiographic data were collected.
Diabetes was characterized by a fasting blood glucose level exceeding 1.26 mg/dL on two separate occasions, each with a 15-day interval between measurements. Statistical analysis was conducted using SPSS software, version 20, with a significance level established at $p < 0.05$.
Inclusion criteria: All patients diagnosed with psoriatic arthritis. Exclusion criteria: Those lost to follow-up.
The investigation made use for citation: Embase, Google Scholar, PubMed, and ResearchGate.
The exploration for pertinent articles encompassed the utilization of the primary term "psoriatic arthritis" in combination with each of the subsequent terms."comorbidities," "diabetes," "cardiovascular disease," "metabolic syndrome," "systemic treatment," "methotrexate," "leflunomide," and "sulfasalazine."

Priority was given to meta-analyses of randomized controlled trials. In cases where such analyses were not available, additional sources were identified by reviewing the references of articles found during the initial search.

## Results:

### a- Description of the Study Population:

Our study encompassed a cohort of 99 individuals diagnosed with Psoriatic Arthritis (PsA). The average age of these patients was 55.16 years, with a standard deviation of ±14.9 years.

The male-to-female sex ratio was 0.41. The average disease duration was 7.56 years +/- 8.8. Diabetes was present in 17.2% of the patients. Renal involvement was observed in 4.8%. Pulmonary involvement was seen in 12.2%. A personal history of psoriasis was found in 28.3% of cases, while a family history of psoriasis was present in 9.2%. 60.2% of the patients was present cutaneous involvement. Hypertension (HTA) was observed in 20.5% of cases, and cardiovascular involvement was noted in 2.3%. Dyslipidemia was present in 23.9% of cases. Inflammatory syndrome was detected in 56% of the patients. Functional impairment was observed in 69.4% of cases. Sacroiliitis on MRI was present in 26.6% of patients. Those receiving methotrexate treatment accounted for 83.5% of the cohort. Unilateral coxitis was identified in 19.6% of cases, and bilateral coxitis was observed in 4.1% of cases. Among the study population, 22.4% of patients were undergoing biologic therapy.

Table 1: Characteristics of the study population, both demographic and clinical-biological, are as follows:

| variables | Value<br>N=99 |
|---|---|
| Age* | 55,16+/-14,94 |
| Age at onset* | 29,12+/- 22,35 |
| Sex***: | |
| • Male | 29,3 |
| • Female | 70,7 |
| Duration of joint involvement** | 5(0-11) |
| History of tuberculosis*** | 9,1 |
| DIABETES*** | 17,2 |
| HYPERTENSION *** | 20,5 |
| DYSLIPIDEMIA *** | 23,9 |
| Personal history of cutaneous psoriasis *** | 28,3 |
| Family history of psoriasis *** | 9,2 |
| Duration of cutaneous psoriasis evolution* | 14,43+/-11,24 |
| Renal involvement *** | 4,8 |
| Pulmonary involvement *** | 12,2 |
| Coxitis *** | 23,7 |
| Activity level *** | 71,3 |
| Functional impact*** | 69,4 |

| | |
|---|---|
| Asdas** | 1,6(0-3,14) |
| DAPSA* | 57,23 +/-46,24690 |
| Inflammatory syndrome. *** | 56,0 |
| FR*** | 48,2 |
| CRP** | 11,65(4-38,75) |
| ACPA*** | 16,2 |
| HLA B27*** | 3,7 |
| SI RX*** | 55,4 |
| NSAIDs,*** | 64,5 |
| CTC *** | 49,5 |
| Duration of Corticosteroid Therapy** | 1(0-5) |
| corticosteroid Bolus*** | 23,7 |
| MTX*** | 83,5 |
| SLZ*** | 15,5 |
| Biotherapy*** | 22,4 |
| HYPERAU*** | 22,5 |
| GOUT*** | 7 |
| uric acid* | 52,46 +/- 26,7667 |
| Op*** | 8,9 |
| Thyroid Dysfunction*** | 11,6 |
| CT* | 1,68 +/- 0,57 |
| HDLc** | 0,46(0,34-0,57) |
| LDLc* | 1,03 +/-0,41 |
| TG* | 1,03+/-0 ,51 |

*expresses mean +/- standard deviation

**expresses median and interquartile range

***expresses in percentage

**b. Description of the population with diabetes :**

Table 2: The demographic and clinical features of the population diagnosed with diabetes are outlined as follows

| variables | with diabete |
|---|---|
| SEXE** : male | 13,8 |
| Female | 18,6 |
| History of tuberculosis ** | 12,5 |
| HTA** | 44,4 |
| DYSLI** | 42,9 |
| Personal history of cutaneous psoriasis *** | 3,6 |
| Family history of psoriasis ** | |
| Activity level ** | 11,1 |
| Functional impact ** | 14,5 |
| PTH | 20,3 |
| Inflammatory syndrome ** | 60 |
| FR** | 19,1 |
| ACPA** | 17,1 |
| HYPERAU** | 36,4 |
| GOUT** | 25,0 |

| | |
|---|---|
| MENOPAUSE** | 16,7 |
| CTC ** | 31,4 |
| Bolus** | 17,4 |
| Age* | 22,7 |
| vitD* | 61,47 +/- 7,77 |
| HDL* | 2,72+/- 1,24 |
| LDL* | 0,43 +/-0,18 |
| CT* | 1,19+/- 0,27 |
| TG* | 1,89+/- 0,37 |
| uric acid * | 1,23+/- 0,53 |
| CRP* | 59,60+/- 31,76 |
| PASI* | 32,85+/-10,23 |
| ASDAS* | 2,86+/-1,01 |
| | 1,21+/-0,81 |

*expresses average +/- standard deviation

** expressed as a percentage

**c. Comparison between the Ankylosing Spondylitis Population with and without Diabetes:**

In bivariate analysis, diabetes was more common in patients who had hypertension (p=0.003), patients with dyslipidemia (p=0.002), those with a personal history of cutaneous psoriasis (p=0.03), patients with a total hip replacement (PTH) (p=0.04), and menopausal patients (p=0.004). Additionally, the mean vitamin D levels were higher in diabetic patients compared to the non-diabetic group. This difference is statistically significant with p=0.04.

This analysis highlights significant associations between diabetes and various factors within the ankylosing spondylitis population, including hypertension, dyslipidemia, personal history of cutaneous psoriasis, PTH, and menopause. Additionally, vitamin D levels were significantly different between diabetic and non-diabetic patients.

Table 3: Contrast between the Two Sets: One with Diabetes and the Other Without.

| variables | with diabete | without diabete | p |
|---|---|---|---|
| SEX** : male | 13,8 | 86,2 | 0,7 |
| Femele | 18,6 | 81,4 | 0,7 |
| History of tuberculosis ** | 12,5 | 87,5 | 1 |
| HYPERTENSION ** | 44,4 | 55,6 | **0,003** |
| DYSLI** | 42,9 | 57,1 | **0,002** |
| Personal history of cutaneous psoriasis ** | 3,6 | 96,4 | **0,03** |
| Family history of psoriasis ** | | | |
| Activity level ** | 11,1 | 88,9 | 1 |
| Functional impact ** | 14,5 | 85,5 | 0,5 |
| PTH ** | 20,3 | 79,7 | 0,2 |
| Inflammatory syndrome ** | 60 | 40 | **0,04** |
| FR** | 19,1 | 80,9 | 0,728 |
| ACPA** | 17,1 | 82,9 | 0,8 |
| HYPERAU** | 36,4 | 63,6 | 0,09 |
| GOUT** | 25,0 | 75,0 | 0,7 |
| MENOPAUSE** | 16,7 | 83,3 | 1 |
| CTC ** | 31,4 | 68,6 | **0,004** |
| Bolus** | 17,4 | 82,6 | 0,8 |

| | | | |
|---|---|---|---|
| AINS ** | 22,7 | 77,3 | 0,5 |
| Age* | 17,2 | 82,8 | 0,8 |
| vitD* | 61,47 +/- 7,77 | 53,85 +/- 15,75 | 0,055 |
| HDL* | 2,72+/- 1,24 | 0,672+/- 0,24 | **0,04** |
| LDL* | 0,43 +/-0,18 | 0,46+/- 0,14 | 0,5 |
| CT* | 1,19+/- 0,27 | 0,99+/- 0,43 | 0,09 |
| TG* | 1,89+/- 0,37 | 1,63+/- 0,60 | 0,1 |
| AU* | 1,23+/- 0,53 | 0,98+/- 0,50 | 0,09 |
| CRP* | 59,60+/- 31,76 | 50,73+/- 25,40 | 0,2 |
| PASI* | 32,85+/-10,23 | 35,13+/-12,54 | 0,8 |
| ASDAS* | 2,86+/-1,01 | 2,62+/-1,32 | 0,9 |
| | 1,21+/-0,81 | 1,75+/-0,73 | 0,3 |

*expresses average +/- standard deviation

** expressed as a percentage

**d. Analysis of Factors Associated with the Occurrence of Diabetes in the Population:**

In a multivariate analysis, HTA and ACPA were significantly associated with the occurrence of diabetes in PsA patients. The results are as follows:

HTA : p=0.002, OR=15.284, 95% Confidence Interval (CI)=2.684-87.028
ACPA : p-value of 0.04, Odds Ratio (OR) of 6.661, with a 95% CI ranging from 1.005 to 44.151.

These results indicate that hypertension and the existence of ACPA are independently linked

to the onset of diabetes in individuals with Psoriatic Arthritis. The odds ratios (OR) and CI offer insights into the robustness and accuracy of these connections.

## Discussion:

Upon comparing individuals with PsA to the broader population, it becomes apparent that they are more prone to an elevated prevalence of type 2 diabetes. Numerous studies have investigated the epidemiological connection between diabetes mellitus (DM)and PsA. The prevalence of DM in individuals with PsA shows variability, ranging from 6.1% to 20.2%. To be more specific, the prevalence of DM in PsA cohorts in regions such as North America, Hong Kong, Israel, Spain, and the United Kingdom exhibits a range. From 11.3% to 20.2%, 18.6%, 15.3%, 9.2% to 13.8%, and 6.1%, respectively [3, 4,5].

This data underscores a noteworthy correlation between Psoriatic Arthritis and the onset of diabetes, indicating a notably higher prevalence of diabetes among individuals with PsA compared to the general population. These findings highlight the importance of monitoring and managing diabetes in individuals with Psoriatic Arthritis, as it represents a common comorbidity that can impact the overall health and well-being of these patients.

In our investigation, we observed a prevalence of 17.2% for DM among individuals with PsA.

The risk of developing DM in individuals with PsA is elevated compared to those without PsA, with the Odds Ratio (OR) ranging from 1.48 in Israel to 9.27 in Hong Kong, respectively [4-8].

These results emphasize that Psoriatic Arthritis is linked to an elevated risk of developing diabetes, and the extent of this risk fluctuates across various regions, as evidenced by varying Odds Ratio (OR) values. This underscores the importance of regular monitoring and preventive measures for diabetes in individuals with Psoriatic Arthritis, as it is a significant comorbidity that can impact their health and quality of life. Further research is necessary to delve into the factors contributing to this elevated risk and to develop tailored strategies for risk reduction and management.

The highest prevalence of DM among individuals with PsA is observed in North America. This occurrence can be attributed, in part, to elevated rates of obesity and unhealthy lifestyles prevalent in the general population [9].

DM between male and female PsA patients. Among the female PsA group, the prevalence of DM was 18.7% (compared to 10.3% in the control group) with an Odds Ratio (OR) of 1.60 (95% Confidence Interval 1.02-2.52). Conversely, in the male PsA group, there was a comparable prevalence of DM (11.2%) in both the PsA group and the control group, with an OR of 0.71 (95% Confidence Interval 0.42-1.22). This study identified an association between Psoriatic Arthritis and DM in female patients but not in male patients. Consequently, the authors suggested that female PsA patients may be more suitable candidates for DM screening [10].

In our investigation, we observed that female PsA patients had a prevalence of 13.8% for DM, while male patients exhibited a higher prevalence of 18.6%. Additionally, Eder et al. explored certain predictive factors for the development of DM. They found that the number of painful joints, with a Hazard Ratio (HR) of 1.53 (95% Confidence Interval 1.08-2.18), and erythrocyte sedimentation rate, with an HR of 1.21 (95% Confidence Interval 1.03-1.41), were predictive of DM development. These findings suggest that patients with elevated disease activity may face an increased risk of developing diabetes [7].

However, our study did not reveal a significant association between diabetes and disease activity (p=0.5). In a cross-sectional study, Queiro et al. observed that in patients with late-onset psoriasis (onset after the age of 40) and Psoriatic Arthritis, diabetes mellitus (DM) was significantly more frequent, with an Odds Ratio (OR) of 8.2 (95% Confidence Interval 1.9 to 12.4). These findings imply that the risk of DM should be carefully evaluated in Psoriatic Arthritis patients whose psoriasis onset occurs after the age of 40 [6].

Overall, these data underscore a heightened prevalence of DM in Psoriatic Arthritis patients compared to the general population. Specifically, the risk of DM appears to be elevated for women and individuals with more active disease, underscoring the importance of vigilant DM screening in these specific populations. In our study, a noteworthy association was identified between diabetes and a personal history of psoriasis (p=0.03).

Recent multicenter cross-sectional studies investigating the link between comorbidities and quality of life in Ankylosing Spondylitis (AS) patients found that anxiety was independently associated with impaired quality of life, while diabetes had no significant effect [11, 12].
Non-steroidal anti-inflammatory drugs (NSAIDs) have undergone extensive research regarding their potential advantages in preventing and treating diabetes. This focus stems from their influence on glucose metabolism. Specifically, NSAIDs exhibit anti-inflammatory effects on pancreatic islets, diminish insulin metabolic clearance, and alleviate hepatic insulin resistance. These actions collectively result in enhanced peripheral glucose absorption and a decrease in endogenous glucose production.

In our study, there was no significant association between diabetes and the use of non-steroidal anti-inflammatory drugs (NSAIDs) (p=0.8).

The likelihood of diabetes induced by glucocorticoids increases in elderly individuals with elevated HbA1c levels and reduced glomerular filtration rates (GFR) [13].
Individuals taking prednisolone in low doses for an extended period exhibit hepatic insulin resistance and decreased non-oxidative peripheral glucose disposal, with no alteration in insulin secretion [14].

Importantly, there is no apparent indication of hyperglycemic effects associated with methotrexate, making it a safe option for individuals with diabetes. Dehpouri et al. conducted a study on PsA patients, revealing that the use of methotrexate did not lead to a significant alteration in HbA1c or fasting blood glucose (FBG) levels [15]. Similarly, a limited retrospective study focusing on patients with diabetes and rheumatologic diseases treated with methotrexate found no significant change in HbA1c before and after treatment [16]. Gisondi et al.'s study on psoriatic patients further confirmed the absence of changes in FBG after 6 months of methotrexate treatment [17]. In a broader retrospective study involving 121,280 patients diagnosed with psoriasis or Rheumatoid Arthritis (RA) and treated with methotrexate, the cohort demonstrated a reduced risk of new-onset diabetes compared to those receiving other non-biologic disease-modifying antirheumatic drugs [18]. Another cohort study reported a decreased risk of diabetes in individuals with psoriasis or RA who were treated with methotrexate [19]. These collective findings strongly suggest that methotrexate does not disrupt homeostasis of glucose in patients with diabetes. However, it is important

to note that despite its favorable effects, methotrexate is linked to a notable elevation in the likelihood of hepatic fibrosis in individuals with diabetes as opposed to those without diabetes [20].

Leflunomide, an inhibitor of pyrimidine synthesis used in the treatment of PsA and other rheumatologic diseases, has demonstrated the ability to control hyperglycemia and enhance insulin sensitivity in murine models [21]. Additionally, it exhibited a protective effect on renal lesions associated with diabetic nephropathy [22]. Importantly, there is currently no evidence indicating that leflunomide might negatively impact glucose homeostasis.

Sulfasalazine exerts its anti-inflammatory effects through diverse mechanisms. A study identified diabetic patients taking sulfasalazine and observed lower HbA1c values during medication use, suggesting potential hypoglycemic effects [23].

Research involving patients with Rheumatoid Arthritis (RA) or Psoriasis (PsO) treated with anti-tumor necrosis factor (TNF) agents (adalimumab, infliximab, and etanercept) for up to 6 months indicated that average glucose levels remained stable [24,25]. Another study revealed a significant reduction in fasting blood glucose in the etanercept-treated group after 6 months compared to the placebo group [26]. These findings imply that anti-TNF treatment within a 6-month timeframe does not adversely affect glucose homeostasis in individuals with Psoriatic Arthritis. In a retrospective cohort study, patients treated with TNF-alpha antagonists exhibited a lower risk of new-onset diabetes compared to those receiving other non-biologic disease-modifying antirheumatic drugs [18]. Case reports and series have suggested recurrent hypoglycemia and improved insulin resistance in patients treated with anti-TNF agents, indicating potential benefits in diabetes management [27–28]. Preliminary evidence suggests that anti-TNF-alpha agents could be safely used in patients with diabetes and might even contribute to improved diabetes outcomes in certain cases.

Regarding Anti-IL-17 and Anti-IL-12/23 Agents, some studies have demonstrated an increase in circulating Th17 cells and elevated IL-17 secretion in diabetes patients. Treatment with anti-IL-17 has been associated with insulin-sensitizing effects [29]. Clinical studies investigating the impact of anti-IL-17 on diabetes and insulin sensitivity have reported no significant difference in fasting blood glucose compared to a placebo [30,31].

In the case of Ustekinumab, a study involving diabetes patients revealed heightened levels of inflammatory cytokines, including IL-23, in pancreatic islets. Treatment with ustekinumab in Psoriatic Arthritis patients led to an increase in fasting blood glucose after 24 weeks of treatment [32].

As for Apremilast, studies on patients with psoriasis and psoriatic arthritis treated with the medication found a neutral impact on glucose tolerance [33–34]. An additional study reported a reduction in HbA1c after 16 weeks of apremilast treatment [35].

## Conclusion:

Our study identified HTA, ACPA, dyslipidemia, menopause, and a personal history of cutaneous psoriasis as predictive factors for the development of diabetes in PsA.

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