ORIGINAL ARTICLE

Association between Oxidative Stress, Cardiovascular Risk, and Disease Activity in Patients with Spondyloarthritis: A Cross-Sectional Study in a Tunisian Cohort

Association entre stress oxydatif, risque cardiovasculaire et activité maladie chez les patients atteints de spondyloarthrite: Une étude transversale dans une cohorte tunisienne

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Abstract

Introduction-Aim: Spondyloarthritis (SpA) is a chronic inflammatory disease associated with an increased cardiovascular (CV) risk that is not fully explained by traditional risk factors. This study aimed to investigate the associations between oxidative stress markers, CV risk profile, and disease activity in a Tunisian cohort of patients with SpA.

Methods: We conducted a monocentric, cross-sectional study involving 101 patients diagnosed with SpA according to the 2009 ASAS criteria. We collected sociodemographic, clinical, and biological data. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP). The CV risk profile was evaluated through anthropometric measurements, lipid profile, homocysteine, and the SCORE2 index. Oxidative stress status was determined by measuring glutathione peroxidase (GPx) activity, serum levels of oligo-elements (copper, zinc, selenium).

Results: The cohort consisted of 101 patients with a mean age of 40.59 ± 11.41 years. A high prevalence of CV risk factors was observed, including overweight/obesity (57.4%), hypertension (31.7%), atherogenic dyslipidemia (73.3% with elevated non-HDL cholesterol), and hyperhomocysteinemia (58.4%). Patients with active disease (ASDAS-CRP ≥ 2.1) exhibited significantly lower GPx activity (p=0.024). Serum copper levels and the copper/zinc (Cu/Zn) ratio were significantly elevated in patients with systemic inflammation (p < 0.001). A significant negative correlation was found between GPx activity and disease activity scores (BASDAI and ASDAS-CRP).

Conclusion: Oxidative stress is closely linked to systemic inflammation and disease activity, with decreased GPx activity and an elevated Cu/Zn ratio emerging as potential biomarkers of inflammatory status.

Keywords: Spondyloarthritis, Oxidative Stress, Cardiovascular Risk, Inflammation, Glutathione Peroxidase (GPx), Tunisia.

Résumé

Contexte : La spondyloarthrite (SpA) est une maladie inflammatoire chronique associée à un risque accru de cardiovascule (CV) qui n'est pas entièrement expliqué par les facteurs de risque traditionnels. Cette étude visait à étudier les associations entre les marqueurs de stress oxydatif, le profil de risque de la CV et l'activité de la maladie chez une cohorte tunisienne de patients atteints de SpA.

Méthodes : Nous avons mené une étude monocentrique et transversale impliquant 101 patients diagnostiqués avec une SpA selon les critères ASAS de 2009. Nous avons collecté des données sociodémographiques, cliniques et biologiques. L'activité de la maladie a été évaluée à l'aide de l'indice d'activité de la maladie de la spondylarthrite ankylosante de Bath (BASDAI) et du score d'activité de la maladie de la spondylarthrite ankylosante avec la protéine C-réactive (ASDAS-CRP). Le profil de risque du CV a été évalué à l'aide de mesures anthropométriques, du profil lipidique, de l'homocystéine et de l'indice SCORE2. Le statut de stress oxydatif a été déterminé en mesurant l'activité de la peroxydase de glutathion (GPx), les niveaux sériques d'oligo-éléments (cuivre, zinc, sélénium).

Résultats : La cohorte comprenait 101 patients avec un âge moyen de 40,59 ± 11,41 ans. Une forte prévalence de facteurs de risque pour la CV a été observée, notamment le surpoids/obésité (57,4 %), l'hypertension (31,7 %), la dyslipidémie athérogène (73,3 % avec un cholestérol non HDL élevé) et l'hyperhomocystéinémie (58,4 %). Les patients atteints de la maladie active (ASDAS-CRP ≥ 2,1) ont montré une activité GPx significativement plus faible (p=0,024). Les niveaux sériques de cuivre et le rapport cuivre/zinc (Cu/Zn) étaient significativement élevés chez les patients souffrant d'inflammation systémique (p < 0,001). Une corrélation négative significative a été trouvée entre l'activité GPx et les scores d'activité de la maladie (BASDAI et ASDAS-CRP).

Conclusion : Le stress oxydatif est étroitement lié à l'inflammation systémique et à l'activité pathologique, avec une diminution de l'activité GPx et un rapport Cu/Zn élevé qui apparaissent comme biomarqueurs potentiels de l'état inflammatoire.

Mot clés: Spondyloarthrite, Stress oxydatif, Risque cardiovasculaire, Inflammation, Peroxydase de glutathion (GPx), Tunisie

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Introduction

Spondyloarthritis (SpA) encompasses a group of chronic inflammatory rheumatic diseases that primarily affect the axial skeleton but can also involve peripheral joints and entheses [1]. The pathophysiology, though not fully elucidated, involves a complex interplay of genetic factors, notably the HLA-B27 antigen, and immune dysregulation [2, 3]. SpA is a systemic condition that significantly impairs quality of life, with a clinical course often marked by flares and periods of remission that can lead to progressive structural damage and functional loss [4].

Beyond its musculoskeletal manifestations, SpA is associated with an increased risk of cardiovascular (CV) disease [5]. This excess risk is not entirely attributable to traditional risk factors like hypertension, dyslipidemia, or smoking, suggesting that disease-specific mechanisms play a pivotal role [6]. Chronic systemic inflammation, a hallmark of SpA, is recognized as a key driver of accelerated atherosclerosis, endothelial dysfunction, and subsequent CV events [7, 8].

In parallel, oxidative stress—defined as an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses—has emerged as a central process in the pathogenesis of chronic inflammatory and cardiovascular diseases [9, 10]. The persistent inflammatory state in SpA can lead to an overproduction of ROS, which in turn can perpetuate inflammation and contribute to tissue damage [11]. Studies have shown that patients with SpA have altered levels of oxidative and anti-oxidative markers compared to healthy individuals [12, 13].

However, data on the interplay between inflammation, oxidative stress, and the comprehensive CV risk profile in SpA patients from North Africa remain scarce. Therefore, this study aimed to evaluate the associations between clinical disease activity, markers of systemic inflammation, oxidative stress status, and the cardiovascular risk profile in a cohort of Tunisian patients with SpA.

Methods

Study Design and Population

A monocentric, cross-sectional study was conducted between September and December 2024 at the rheumatology department of the Military Hospital of Tunis. We enrolled 101 consecutive patients aged 18 years or older who met the Assessment of SpondyloArthritis international Society (ASAS) 2009 classification criteria for SpA and had a disease duration of at least six months. Patients with uncontrolled cardiovascular or metabolic diseases (e.g., recent myocardial infarction, unstable angina, uncontrolled diabetes), or those taking high-dose corticosteroids or antioxidant supplements, were excluded. The study protocol conformed to the Declaration of Helsinki and received approval from the local ethics committee. All participants provided written informed consent.

Data Collection

A standardized form was used to collect data through patient interviews, clinical examinations, and medical record reviews.

Clinical and Functional Assessment:
Sociodemographic data, SpA phenotype (axial, peripheral, or mixed), disease duration, and extra-articular manifestations were recorded. Disease activity was assessed with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP). Functional status and mobility were evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI) and Metrology Index (BASMI). Quality of life was measured with the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire, and anxiety and depression were screened using the Hospital Anxiety and Depression Scale (HADS).

Cardiovascular Risk Assessment:
Anthropometric measurements included Body Mass Index (BMI) and waist-to-hip ratio (RTH). Blood pressure was measured after a 30-minute rest. A fasting blood sample was collected to determine the lipid profile (total cholesterol, HDL, triglycerides) and plasma homocysteine. The 10-year risk of fatal and non-fatal CV events was calculated using the SCORE2 algorithm [14].

Inflammatory and Oxidative Stress Markers:
Systemic inflammation was assessed by measuring C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). For oxidative stress assessment, whole blood glutathione peroxidase (GPx) activity was measured using a spectrophotometric kinetic method. Serum concentrations of copper (Cu), selenium (Se), and zinc (Zn) were determined using inductively coupled plasma mass spectrometry (ICP-MS) or atomic absorption spectrometry (SAA). Other markers, including ceruloplasmin, haptoglobin, bilirubin, and uric acid, were also assayed. Serum 25-hydroxyvitamin D [25(OH)D] was measured to assess vitamin D status.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0. Continuous variables were presented as mean ± standard deviation or median [interquartile range], while categorical variables were presented as frequencies and percentages. Group comparisons were made using Student's t-test, Mann-Whitney U test, or the chi-square test as appropriate. Correlations were assessed using Pearson or Spearman coefficients. A p-value of < 0.05 was considered statistically significant.

Results

Patient and Disease Characteristics

A total of 101 patients were included, with a mean age

of 40.59 ± 11.41 years and a strong male predominance (83.2%). The median age of disease onset was 32 years. The cohort comprised 58.4% with axial SpA, 36.6% with mixed (axial and peripheral) SpA, and 5.0% with pure peripheral SpA. The mean BASDAI was 2.39 ± 1.68, and the mean ASDAS-CRP was 2.06 ± 1.16, with 48.5% of patients having active disease (ASDAS-CRP ≥ 2.1). Radiological damage was significant, with a median total BASRI score of 6 [0-16]. NSAIDs were prescribed in 60.4% (n=61).

Corticosteroids were used in 3 patients (2.97%) at a mean dose of 9.16 mg/day [7.5–10].

csDMARDs were prescribed 20.8% (n=21). Methotrexate was used in 15 patients at a mean dose of 14.61 mg/week [10–20], and sulfasalazine in 6 patients at a mean dose of 2.25 g/day [1.5–3]. Forty-seven patients were receiving anti-TNFα therapy.

Cardiovascular Risk Profile

The prevalence of CV risk factors was high: 57.4% of patients were overweight or obese (BMI ≥ 25 kg/m ²), 31.7% had hypertension, and 58.4% had hyperhomocysteinemia (>12 µmol/L). The lipid profile was atherogenic, with 73.3% of patients having non-HDL cholesterol levels above recommended targets. The median 10-year CV risk estimated by SCORE2 was 6.95%, indicating a moderate-to-high risk population.

Inflammatory and Oxidative Stress Status

Elevated markers of systemic inflammation were common, with 30% of patients having a positive CRP (>8 mg/L) and 85.3% having an elevated ESR (>20 mm/h).

Regarding oxidative stress, 83.9% of patients had GPx activity above the normal reference range. However, GPx activity was significantly lower in patients with clinically active disease (BASDAI ≥ 4, p=0.017) and biologically active disease (ASDAS-CRP ≥ 2.1, p=0.024) (Figure 7).

Patients with a positive CRP had significantly higher serum copper levels ($p < 0.001$), ceruloplasmin ($p < 0.001$), and Cu/Zn ratio ($p < 0.001$) compared to those with a negative CRP. Zinc and selenium levels did not differ significantly based on inflammatory status. A marked vitamin D deficiency (<30 µg/L) was found in 90.5% of patients.

Correlations

A significant, albeit weak, negative correlation was observed between GPx activity and both BASDAI ($r = -0.213$, $p = 0.041$) and ASDAS-CRP ($r = -0.266$, $p = 0.01$). A strong positive correlation was found between serum copper and ceruloplasmin ($r = 0.842$, $p < 0.001$). Furthermore, cardiovascular risk factors were correlated with disease characteristics; for instance, diastolic blood pressure correlated positively with disease duration ($r = 0.298$, $p = 0.003$), and RTH correlated with age of disease onset ($r = 0.391$, $p < 0.001$).

Discussion

This study provides a comprehensive assessment of the interplay between disease activity, oxidative stress, and cardiovascular risk in a Tunisian SpA cohort. Our findings confirm a high burden of CV risk factors in these patients, consistent with previous reports highlighting SpA as an independent risk factor for cardiovascular disease [15, 16]. The high prevalence of atherogenic dyslipidemia, hyperhomocysteinemia, and abdominal obesity underscores a pro-atherosclerotic metabolic environment, likely amplified by chronic systemic inflammation [17, 18]. No significant differences in oxidative stress marker levels were observed between patients treated with anti-TNFα, csDMARDs, or corticosteroids and those not receiving these therapies. (Table I).

Table 1. Comparison of oxidative stress biomarkers according to ongoing treatments

		Cu	Zn	Cu/Zn ratio	GPx
NSAIDs	No	20.1 ± 6.4	11.6 ± 2.1	1.8 ± 0.9	24 294.5 ± 23 089.6
	Yes	20 ± 4	11.8 ± 2.2	1.8 ± 0.5	19 861.9 ± 15 932.9
	P	0.923	0.679	0.655	0.271
anti-TNFα therapy	No	20.1 ± 4	11.8 ± 2.2	1.8 ± 0.5	19 892.4 ± 16 985.4
	Yes	19.9 ± 6.1	11.7 ± 2.1	1.8 ± 0.8	23 491.1 ± 21 205
	P	0.849	0.705	0.788	0.362
CsDMARDs	No	19.8 ± 5.1	11.9 ± 2.1	1.7 ± 0.7	22 280.3 ± 19 572.3
	Yes	20.9 ± 5.1	11.1 ± 2.3	2 ± 0.7	19 215 ± 17 612.7
	p	0.408	0.132	0.145	0.527
Corticosteroids	No	20 ± 5.1	11.8 ± 2.1	1.8 ± 0.7	21 854.7 ± 19 273.2
	Yes	21.3 ± 2.3	11.8 ± 4.6	2 ± 0.9	11 416 ± 1 612.2
	p	0.656	0.972	0.544	0.448

Cu: Copper; **Zn**: Zinc; **GPx**: Glutathione peroxidase

A key finding of our study is the inverse relationship between GPx activity and SpA disease activity. While most patients had GPx levels above the normal laboratory range, those with higher inflammatory and clinical activity scores exhibited significantly lower enzymatic activity. This suggests a consumption of antioxidant defenses in response to the heightened oxidative stress generated by active inflammation. This finding aligns with the hypothesis that oxidative stress is not merely a bystander but an active participant in the pathophysiology of SpA, potentially contributing to the perpetuation of inflammation and tissue damage [19]. The observed negative correlation between GPx and ASDAS-CRP, a more objective measure of inflammation than BASDAI, further strengthens this link.

Our results also highlight the utility of the serum Cu/Zn ratio as a biomarker of systemic inflammation. The significant increase in copper, an acute-phase

reactant, and the resultant elevation of the Cu/Zn ratio in patients with high CRP levels reflect the intensity of the inflammatory process. This is consistent with literature proposing this ratio as a composite marker of inflammation and oxidative stress [20]. In contrast, serum zinc levels were not associated with disease activity, suggesting its measurement alone may be less informative in this context.

The study has several strengths, including its detailed, multi-faceted assessment of a well-characterized cohort, making it the first of its kind in the region. However, limitations must be acknowledged. The cross-sectional design precludes causal inferences, and the relatively modest sample size from a single center may limit generalizability. Furthermore, our assessment of oxidative stress was limited to a few key markers and did not include direct measures of oxidative damage.

Conclusion

In conclusion, this study demonstrates a significant cardiovascular risk burden in Tunisian patients with SpA, characterized by a high prevalence of metabolic abnormalities. We established a clear link between systemic inflammation, disease activity, and oxidative stress, evidenced by the consumption of GPx antioxidant defenses and an altered oligo-element balance in active disease. Markers such as GPx activity and the Cu/Zn ratio may serve as valuable complementary tools for monitoring the inflammatory state in SpA. These findings reinforce the necessity for proactive and comprehensive cardiovascular risk management as an integral part of the care for patients with spondyloarthritis.

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