Original Article

Obesity, Lipid Profile and Cytokines in Spondyloarthritis

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Abstract

Context: Chronic rheumatic diseases seem to be associated with a higher risk of developing cardiovascular diseases. The link between cytokines and lipid profile in spondyloarthritis is not well elucidated. **Aims:** We aimed to assess the relationship between cytokines and obesity, lipid profile and atherogenic indexes in spondyloarthritis. **Methods and Material:** We conducted a cross-sectional study including 45 patients with axial radiographic spondyloarthritis. For each patient, we measured the following pro-inflammatory cytokines: interleukin (IL-) 1, IL-8, IL-6, IL-17, IL-23 and tumor necrosis factor α (TNFα), and anti-inflammatory cytokines: IL-10. We also measured total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLc) and low-density lipoprotein cholesterol (LDLc). We calculated the following ratios: TC/HDLc, TG/HDLc, LDLc/HDLc and Log[TG/HDLc]. **Statistical Analysis Used:** SPSS. **Results:** The mean age was 46 ± 11.9 years. IL-8 levels were increased in obese patients ($P = 0.003$). IL-8 and IL-22 levels were significantly higher in patients with abdominal obesity ($P = 0.024$ and $P = 0.042$, respectively). IL-6 levels were lower in patients with hypercholesterolemia ($P = 0.009$). IL-1 levels correlated to TG (r = 0.413; $P = 0.005$). IL-1 and IL-6 were correlated to TG/HDLc (IL-1: r = 0.484, $P = 0.001$; IL-6; r = 0.700, $P = 0.012$) and Log[TG/HDLc] (IL-1: r = 0.354; $P = 0.012$; IL-6: r = 0.309, $P = 0.041$). IL-10 level was correlated to TC/HDLc (r = 0.333, $P = 0.027$) and LDLc/HDLc (r = 0.342, $P = 0.023$). **Conclusions:** IL-8 and IL-22 were higher in patients with abdominal obesity, highlighting the contribution of the adipocytes to the secretion of pro-inflammatory cytokines. The correlation between cytokines and atherogenic indexes suggests the role of these cytokines in the occurrence of cardiovascular diseases in spondyloarthritis.

Keywords: Atherogenic indexes, axial spondyloarthritis, cardiovascular risk, cytokines, obesity

Introduction

The increased cardiovascular risk in patients with rheumatic diseases has been reported by several studies.[1,2]

It can be explained by the inflammatory process. Indeed, inflammation promotes the effects of conventional risk factors and plays a crucial role in all phases of atherosclerosis.[3] Pro-inflammatory cytokines, which are implicated in the pathogenesis of rheumatic inflammatory diseases, seem to induce atherosclerosis and cardiovascular events.[4] Moreover, the tumor necrosis factor α (TNFα) promotes insulin resistance by decreasing tyrosine kinase activity of the insulin receptor and consequently reducing insulin activity.[5]

Rheumatoid arthritis and psoriatic arthritis were considered independent cardiovascular risk factors. Likewise, atherosclerosis-related diseases were the first cause of mortality in rheumatoid arthritis.[6] Obesity, lipid profile and atherogenic indexes are less studied in axial spondyloarthritis (SpA).[7] The SpA is an inflammatory rheumatic disease mainly affecting the spine and sacroiliac joints.[8] Apart from genetic predisposing,[9] pro-inflammatory cytokines play a role in the pathophysiology of SpA.[10,11]

Overweight and obesity are common in SpA patients. They seem to be associated with high disease activity.[12]

Furthermore, atherogenic indexes were higher in SpA patients.[7] Several studies showed that the atherogenic index of plasma (AIP) is more reliable to assess lipid profile in SpA,[13,14] especially when other atherogenic risk parameters are normal. This index can predict cardiovascular events.[15]

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There is growing evidence regarding the role of inflammation in promoting cardiovascular risk. However, data regarding the link between pro-inflammatory cytokines, obesity and lipid profile in SpA are scarce.

We aimed to study the link between the pro and anti-inflammatory cytokines, obesity, lipid profile and atherogenic indexes in SpA patients.

Subjects and Methods

Study design

We conducted a cross-sectional study, including patients followed for radiographic axial SpA from 2020 to 2021.

This study was carried out in the outpatient department of Rheumatology. Immunological exams were performed in the department of immunology of the same hospital.

Inclusion criteria

We included consecutive patients followed for radiographic axial SpA according to the Assessment of Spondylarthritis International Society (ASAS) 2009 classification criteria.[16]

Non-inclusion criteria

We did not include patients with type 1 diabetes; diseases or treatment interfering with lipid metabolism (cirrhosis, liver failure, evolutive neoplasm, malabsorption disorders, long-term corticosteroids, non-selective beta-blockers, retinoids, ciclosporin, tacrolimus, estrogen, thiazide diuretic and antiretroviral drugs); secondary dyslipidemia[17] caused by hypothyroidism, chronic kidney disease, nephrotic syndrome, pregnancy, cholestatic liver disease and those with conditions that may overestimate waist circumference measurements (ascites, white line, umbilical hernia, eventrations and visceromegaly).

We excluded patients with a history of familial dyslipidemia,[18] infection and auto-immune diseases.

Clinical assessment

We collected demographic and clinical data, including age, gender, disease duration, smoking, extra-articular manifestations and therapeutic management.

Disease activity was assessed using the Spondylitis Disease Activity Index (BASDAI)[19] and the Ankylosing Spondylitis Disease Activity Score ($ASDAS_{CRP}$).[20]

Using $ASDAS_{CRP}$, SpA is active when this score is higher than 2.1.

Using BASDAI, the SpA is considered active when the BASDAI score is higher than 4.

Body mass index (BMI) was measured before the clinical examination. It is calculated as a person's weight in kilograms divided by the square of the person's height in meters (kg/m²) and interpreted according to the World Health Organization classification of BMI.[21]

The waist circumference was assessed with a tape measure midway between the lower rib margin and the iliac crest.[22] According to the 2009 International Diabetes Federation (IDF) criteria,[23] abdominal obesity was defined as a waist circumference ≥94 cm for men and ≥80 cm for women).

Biological assessment

Peripheral blood samples were taken after an overnight fast.

The lipid profile was assessed by measuring: total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL_c) and low-density lipoprotein cholesterol (LDL_c).

Lipid profile parameters were measured using D*C 700 Au Beckman Coulter. Different measurement methods were used: Immune-inhibition for HDLc, glycerol phosphate oxidase-p-aminophenazone (GPO-PAP) method for TG and cholesterol oxidase phenol 4-aminoantipyrine peroxidase (CHOD-PAP) method for TC and LDL_c.

We calculated the following ratios: TC/HDL_c, TG/HDL_c, LDL_c/HDL_c and the AIP (Log [TG/HDL_c]). Using the AIP, the cardiovascular risk is low when this index is −0.3 to 0.1, medium 0.1 to 0.24 and high when above 0.24.[24]

The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) were measured for each patient. CRP positive threshold was 8 mg/L or more.

We measured pro-inflammatory cytokines, including IL-1, IL-8, IL-6, IL-17, IL-22, IL-23, and TNFα and anti-inflammatory cytokine (IL-10).

IL-1, IL-8, IL-6 and TNFα were measured using chemiluminescence. IL-10, IL-17, IL-22 and IL-23 were measured using the ELISA technique (enzyme-linked immunosorbent assay).

Statistical analysis

We performed statistical analysis using the Statistical Package for Social Sciences (SPSS) version 25.

We used descriptive statistics to identify the characteristics of the study population. Continuous variables were presented as the mean ± standard deviation (SD). We compared categorical variables and continuous ones using Mann–Whitney U test. Correlations were tested using Pearson or Spearman correlations, depending on data distribution. The significance level was set at a P value <0.05.

Ethical consideration

This study was approved by the ethics committee of the Hospital. Consent was signed by patients after informing them of the aims of the study and data collection methods.

Results

Characteristics of SpA patients

We included 45 patients: 37 men and 8 women. Table 1 summarizes the clinical characteristics of axial SpA patients. A BMI ≥25 kg/m² was noted in 19 patients (42.2%).

Using $ASDAS_{CRP}$, 11% of patients had inactive disease (n = 5). Using BASDAI, the active disease was noted in 42% of

Table 1: Clinical characteristics of patients

Clinical characteristics	Means or percentages
Age, mean±SD years	46±11.9
Disease duration, mean±SD months	113.21±99
BMI, mean±SD kg/m^2	25.7±5.1
BMI ≥25 kg/m^2 (*n* (%))	23 (51%)
Smoking (*n* (%))	24 (54%)
Family history of SpA (*n* (%))	2 (4%)
Personal history	
Type 2 diabetes (*n* (%))	4 (9%)
Hypertension (*n* (%))	4 (11%)
Ulcer (*n* (%))	3 (7%)
Tuberculosis (*n* (%))	2 (4%)
Extra-articular manifestations of SpA	
Psoriasis (*n* (%))	21 (53%)
IBD (*n* (%))	17 (40%)
Ophthalmic (*n* (%))	3 (7%)
Cardiac (*n* (%))	12 (27%)
Pulmonary involvement (*n* (%))	3 (7%)
Renal involvement (*n* (%))	10 (22%)
	3 (7%)
Clinical assessment	
BASDAI, mean±SD	3.7±2
$ASDAS_{CRP}$, mean±SD	2.77±1.2
Treatment	
NSAIDs (*n*, (%))	37 (86%)
Methotrexate (*n*, (%))	15 (37%)
Sulfasalazine (*n*, (%))	16 (38%)
TNFα inhibitor (*n*, (%))	17 (42%)

EAM: Extra-articular manifestations, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Score Index, IBD: Inflammatory bowel disease, NSAID: Non-steroids anti Inflammatory drugs, TNF: Tumor necrosis factor, BMI: body mass index

cases (n = 19) and the BMI was higher in patients with active disease (27.53 ± 4.88 vs 24.39 ± 5.11 kg/m²).

Biological parameters

Biological parameters were summarized in Table 2.

Hypercholesteremia was found in 19 patients (42.2%). Hypertriglyceridemia was noted in seven cases (15.6%). HDL_c was low in 21 patients (46.7%).

According to the AIP stratification, 28 (62%) subjects had low cardiovascular risk, 9 (20%) at medium risk and 8 (18%) at high risk.

Comparison of interleukins depending on the presence of obesity and lipid profile abnormalities

IL-8 levels were higher in patients with abdominal obesity (19.17 ± 27.03 vs 10.90 ± 12.76 pg/mL, $P = 0.024$) and obesity (16.21 ± 9.6 vs 14.05 ± 32.75 pg/mL, $P = 0.003$). IL-22 levels were also higher in patients with abdominal obesity (49.56 ± 34.92 vs 31.23 ± 19.42 pg/mL, $P = 0.042$).

IL-6 levels were lower in patients with hypercholesterolemia (3.32 ± 2.75 vs 21.62 ± 51.64 pg/mL, $P = 0.009$).

However, there was no difference in cytokine between patients with normal or abnormal TG and HDLc.

Correlations between interleukins and lipid parameters

As shown in Table 3, a positive correlation was found between IL-1 levels and: TG level (r = 0.413; $P = 0.005$), TG/HDL_c (r: 0.484; $P = 0.001$), and $Log[TG/HDL_c]$ (r = 0.354; $P = 0.018$).

Moreover, a positive correlation was found between IL-6 levels and TG/HDL_c (r = 0.70; $P = 0.012$) and $Log[TG/HDL_c]$ (r = 0.309; $P = 0.041$).

IL-10 levels correlated to TC/HDL_c (r = 0.333, $P = 0.027$) and LDL_c/HDL_c ratios (r = 0.342, $P = 0.023$).

Discussion

We attempted to determine the link between cytokines and obesity, lipid profile and atherogenic indexes in SpA patients.

We found that the BMI was higher in patients with active disease. The mechanism explaining how obesity influences disease activity is not clear.[12] It can be due to the high secretion of pro-inflammatory cytokines. Indeed, IL-8 and IL-22 levels were significantly higher in patients with obesity and abdominal obesity. Similarly, IL-22 levels were higher in patients with abdominal obesity.

Several studies demonstrated that cytokines produced by the IL-17/IL-23 axis were higher in SpA patients than in healthy controls,[25,26] suggesting the role of pro-inflammatory cytokines in the physiopathology of axial SpA.[27,28]

These pro-inflammatory cytokines, especially IL-6, TNFα[29-32] and IL-8[33] correlated to BMI. This finding was explained by the contribution of adipocytes to the secretion of pro-inflammatory cytokines (TNFα, IL-6, IL-12, IL-23 and IL-17).[34]

Likewise, obesity induces modification in the balance between pro-inflammatory (T helper 1 and T helper 17 lymphocytes) and anti-inflammatory (T helper 2 and regulatory T lymphocytes) CD4+ cells subsets, leading to secretion of cytokines from newly recruited adipose tissue macrophages. Consequently, the secretion of IL-17A increases, potentializing the inflammatory cytokine profile in SpA patients.[35]

No correlation was found between BMI and IL-17 or IL-23. The IL-17 and IL-23 levels were higher in these patients with obesity.[36]

There are controversial results regarding the link between IL-22 and abdominal obesity.

Previous studies suggested that higher endogenous circulating IL-22 may be associated with higher levels of several cardiometabolic risk factors in the mouse models. IL-22 effects were anti inflammatory and anti diabetic.[37] However, Brito-Luna *et al*.[38] found that waist circumference correlated negatively with IL-22 levels in psoriatic patients with metabolic syndrome.

The levels of chemokines, such as IL-8, were increased in obese subjects compared to the control group. The authors suggested that IL-8 contributes to obesity-related metabolic complications, atherosclerosis and diabetes.[39]

Table 2: Biological characteristics of patients

Parameters [reference range]	Means or percentages
Biological inflammatory biomarkers levels	
ESR (mm)	41.18±34
CRP (mg/L) [<8]	29.2±39.61
CRP≥8 mg/L (*n* (%)	22 (49%)
Cytokines levels	
IL-1 (pg/mL) [<5]	10.88±23.1
IL-1≥5 (*n* (%))	41 (91%)
IL-6 (pg/mL) [<5.9]	13.89±42.4
IL-6≥5.9 (*n* (%))	12 (27%)
IL-8 (pg/mL) [<62]	14.58±20.47
IL-8≥62 (*n* (%))	2 (4%)
IL-17 (pg/mL) [<5]	91.7±80.4
IL-17≥5 (*n* (%))	42 (93%)
IL-22 (pg/mL) [<15]	39.37±28.58
IL-22≥15 (*n* (%))	35 (78%)
IL-23 (pg/mL) [<15]	17.26±16.9
IL-23≥15 (*n* (%))	21 (47%)
TNFα (pg/ml) [<8.1]	24.84±45.33
TNFα ≥ 8.1 (*n* (%))	22 (49%)
IL-10 (pg/mL) [<15]	11.01±20.1
IL-10≥15 (pg/mL) (*n* (%))	11 (24%)
Lipid profile	
TC (mmol/L) [>5.17]	4.6±0.98
TC≥5.17 (*n* (%))	13 (29%)
TG (mmol/L) [>1.7]	1.27±0.52
TG≥1.7 (*n* (%))	7 (16%)
LDL_c (mmol/L) [>4.1]	2.89±0.83
LDL_c≥4.1 (*n* (%))	4 (9%)
HDL_c (mmol/L) [<1]	1.10±0.31
HDL_c<1 (*n* (%)	20 (44%)
Atherogenic indexes	
TC/HDL_c	4.3±1.25
TG/HDL_c	1.20±0.62
LDL/HDL_c	2.77±1.05
Log [TG/HDL]	0.024±0.23

Values were expressed as mean±SD, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, IL: Interleukin, TNFα: Tumor necrosis factor alpha, TC: Total cholesterol, TG: triglyceride LDLc; low-density lipoprotein cholesterol , HDLc: high density lipoprotein

Furthermore, several reports showed that increased IL-8 levels were associated with an increased risk of cardiovascular disease and acute cardiovascular events.[40,41] Indeed, IL-8 is involved in the firm adhesion of rolling monocytes in the early stages of atherogenesis.[42]

Our study was in line with Kim *et al*.[39] who found a correlation between IL-8 and waist circumference, highlighting the role of visceral in the secretion of IL8 in patients with obesity.

Data about the link between lipid profile abnormalities and pro-inflammatory cytokines are contradictory.

A positive correlation was also noted between TG level and IL-1 level (r = 0.413; $P = 0.005$).

Increased cytokine levels can lead to lipid profile perturbation.[43] This goes along with the fact that saturated fatty acids, potentially acting via toll-like receptor 4, drive classical macrophage activation in the obese state.[44]

It has been reported that high IL-6 levels were associated with insulin resistance and atherosclerosis, thus inducing an increased risk of type 2 diabetes, hypertension or dyslipidemia.[31,45] IL-6 was strongly correlated with systolic blood pressure and TC level.[46]

Nevertheless, TC levels were lower in patients with high levels of IL-6 during acute inflammation.[47] Our study supports this finding in SpA patients showing that IL-6 was lower in those with hypercholesterolemia. Treatment with IL-6 inhibitors in patients with rheumatoid arthritis led to an elevation in TC, LDL_c and HDL_c levels. However, cardiovascular events occurring under this treatment were in the range of what is expected in rheumatoid arthritis.[48]

The link between dyslipidemia and pro-inflammatory cytokines (IL-17 and IL-23) was less studied. Manti *et al*.[49] found a positive correlation between these cytokines and lipid parameters (CT, LDLc and TG).

These findings suggest that TC is not a reliable marker for assessing cardiovascular risk in patients with SpA, hence the importance of atherogenic indexes in these patients.[50]

Table 3: Pearson's correlation between biological parameters

	TC/HDL	TG/HDL	LDL/HDL	Log[TG/HDL]	LDLc	HDLc	TG	TC
IL-1	0.126	0.484**	0.163	0.354*	0.072	−0.148	0.413**	−0.017
IL-6	0.070	0.370*	0.106	0.309*	−0.039	−0.194	0.265	−0.142
IL-8	−0.103	−0.015	−0.132	−0.023	−0.069	0.072	0.013	−0.048
IL-17	0.110	0.118	0.117	0.102	0.067	−0.018	0.037	0.046
IL-22	−0.213	−0.129	−0.244	−0.096	−0.220	0.108	−0.141	−0.177
IL-23	−0.172	−0.210	−0.171	−0.203	0.044	0.236	0.095,	0.147
TNFα	−0.228	−0.098	−0.279	−0.172	−0.200	0.189	0.236	−0.022
IL-10	0.333*	0.109	0.342*	0.328	0.241	0.118	0.636	0.643

Date are presented as the *r* value in Pearson's correlation test * $P<0.05$, ** $P<0.01$, *** $P<0.001$. IL: Interleukin, TNFα: Tumor necrosis factor alpha, TC: Total cholesterol, TG: triglyceride LDLc; low-density lipoprotein cholesterol , HDLc: high-density lipoprotein

Our study showed that TG/HDL_c and Log [TG/HDL_c] correlated to IL-1 and IL-6 levels. Thus, AIP is more reliable in evaluating the lipid profile in SpA.

Interestingly, we found that the IL-10 level was correlated to TC/HDL_c and LDL_c/HDL_c ratios. The role of IL-10 in inflammatory diseases is still enigmatic. Although known as an anti-inflammatory cytokine,[51] recent data showed that high IL-10 levels were associated with an increased risk of the acute coronary syndrome,[52] higher levels of TG and severe HDL_c deficiency,[53] especially in obese patients.

This finding suggests that in pathological conditions, such as systemic inflammation, IL-10 seems to have pro-inflammatory properties and thereby, promotes atherogenesis. Cardiovascular risk can be predicted by both pro-inflammatory and anti-inflammatory cytokines plasma levels.

Our study has limitations. The uncontrolled open design study with small sample size. Moreover, we did not assess the carotid intima-media thickness or coronary calcium scores.

Conclusion

The BMI was higher in patients with active SpA. IL-8 and IL-22 were higher in patients with obesity or abdominal obesity, highlighting the contribution of the adipocytes in the secretion of these cytokines.

The correlation between cytokines and atherogenic indexes suggests the role of these cytokines in the occurrence of cardiovascular diseases in SpA patients.

This finding argues for obesity management in SpA patients to achieve disease remission, reduce the secretion of cytokines and avoid lipid profile abnormalities.

Authors' contributions

- Maroua SLOUMA has substantively revised the work
- Wided LAHMAR and Lobna KHARRAT have drafted the work
- Khaoula BEN ALI and Aymen TEZEGHDENTI has contributed to the data collection
- Rim DHAHRI and Leila METOUI have made substantial contributions to the analysis of data
- Ezzedine GHAZOUANI has made substantial contributions to the design of the work
- Imen GHARSALLAH and Bassem LOUZIR have made substantial contributions to the conception of the work

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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