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Micronutrients deficiencies in patients with spondylarthritis: the potential immunometabolic crosstalk in disease phenotype

P. TRIGGIANESE[1], F. CASO[2], D. DELLA MORTE[3,4], A. D'ANTONIO[1], S. FERRIGNO[1], M. FATICA[1], L. COSTA[2], M. TASSO[2], P. CONIGLIARO[1], A. BERGAMINI[1], M.S. CHIMENTI[1]

[1]Rheumatology, Allergology and Clinical Immunology, Department of "Medicina dei Sistemi", University of Rome Tor Vergata, Rome, Italy
[2]Rheumatology Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy
[3]Department of Human Sciences and Quality of Life Promotion, San Raffaele Rome Open University, Rome, Italy
[4]Department of "Medicina dei Sistemi", University of Rome Tor Vergata, Rome, Italy

Abstract. – OBJECTIVE: Micronutrient deficiencies (MNDs) are common among patients with certain chronic inflammatory diseases. They are associated with a pro-inflammatory status and co-morbidities. However, no studies have specifically investigated MNDs in Spondyloarthritis (SpA). This paper aimed at analyzing the occurrence of anemia and deficiencies of ferritin (Fe), vitamin D [25(OH)D], vitamin B12 (B12), and folic acid (FA) in SpA patients. The interplay of MNDs with age, gender, and metabolic abnormalities was also explored.

PATIENTS AND METHODS: MNDs were evaluated in 220 SpA outpatients (137 females and 83 age-matched males) with psoriatic arthritis (PsA, n=110) and non-psoriatic SpA (n=110). Metabolic parameters were analyzed. Disease activity was assessed by either Disease Activity in PSoriatic Arthritis (DAPSA) or Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP) as appropriate, while the functional status was evaluated using Health Assessment Questionnaire modified for SpA (HAQ-S).

RESULTS: Anemia occurred in 13.6% of subjects of the study cohort and almost wholly in females (p=0.004). Females showed higher Fe deficiency (p=0.04) and lower Fe levels (p=0.0003) than males. Hemoglobin (Hb) resulted inversely related to age and CRP (p=0.01 and p=0.008) in male group. The 25(OH)D deficiency (≤20 ng/ml) was present in 23.2% of the cohort with a higher prevalence in males than females (p=0.02): moreover, 25(OH)D inversely correlated with disease duration (p=0.02) in males. The B12 deficiency (≤200 pmol/l) was rare (13.2%), while FA ≤4 ng/ml was frequent (22%) and associated with B12 deficiency in 31% of cases. SpA patients in moderate/high disease activity had higher Body Mass Index (BMI) (p=0.04) and HAQ-S (p<0.0001), as well as lower Hb (p=0.02), and Fe (p=0.03) than patients in remission/low disease activity (LDA). In patients with extra-articular manifestations, female sex was prevalent (F:M=2) and B12 levels were lower than in patients without (p=0.005). Interestingly, 25(OH)D was lower (p=0.04) and both BMI and HAQ-S (p=0.036 and p=0.01) were higher in patients without extra-articular involvement than patients with.

CONCLUSIONS: Our findings documented a relevant prevalence of MNDs in SpA patients, and its strict interplay with gender and metabolic abnormalities by highlighting the role of MNDs in inflammatory-dependent dysmetabolism in SpA.

Key Words:
Inflammation, Metabolism, Micronutrient, Obesity, Spondyloarthritis.

Introduction

Micronutrients are vitamins and minerals that have an important role in body's health, since they are involved in production of enzymes, hormones, and other substances essential for normal growth and body development[1]. Indeed, micronutrients play an important role in immunomodulatory processes through their interactions

Corresponding Author: Paola Triggianese, MD, Ph.D; e-mail: triggianese@med.uniroma2.it

with both innate and adaptative immunity and influencing pro-/-anti-inflammatory cytokines balance[2-4]. Emerging evidence[5,6] supports a beneficial role of vitamin D [25(OH)D], folic acid (FA), and metabolically related B-vitamins in bone health of generally healthy subjects. Micronutrients serum levels depend on multiple factors, such as nutrition, gut microbiome, age, and gender[7]. Gender difference also affects colon luminal environment, which is in turn dependent on B-vitamins status[8].

Micronutrients deficiencies (MNDs) lead to several pathologic conditions, most of them starting as subclinical phenotypes[9,10]. Among such pathological conditions it is possible to list: anemia related to lower iron, FA, and vitamin B12 (B12) levels; reduced bone mineral density mainly related to low calcium and 25(OH) D); high risk of pro-thrombotic state, linked to FA and B12; and chronic bowel inflammation, in which FA, calcium and 25(OH)D play a key role in the pathogenesis[11]. MNDs have been documented to be common among patients with chronic inflammatory diseases, as well as autoimmune disorders[12,13]. In these conditions, MNDs are thought to be associated with a heightened inflammatory status and cause of co-morbidities[14,15]. Moreover, evidence[16] on epigenetic influences and the likely influence of MNDs on fetal origins of adult chronic diseases are currently under investigation. The most common MNDs include iron, 25(OH)D, B12, and FA deficiencies. Some studies[19-21] have proved a significantly higher prevalence of these specific MNDs in chronic autoimmune diseases, mainly inflammatory bowel disease (IBD)[17,18]. Furthermore, MNDs commonly lead also to cutaneous abnormalities involving skin, hair, and nails, with psoriasis (PsO) being included.

However, the relationship between MNDs and inflammatory arthritis is at least controversial, and only some data have been recently reported on 25(OH)D and rheumatoid arthritis (RA)[22-24]. To the best of our knowledge, no previous studies have investigated MNDs in Spondyloarthritis (SpA) patients. Specifically, the relationship between MNDs and SpA can be complex because MNDs could act as factor associated to possible extra-articular involvement in SpA (e.g., IBD, PsO, others), leading to increased risk of inflammation.

Hence, the main aims of the current study were to examine the prevalence of MNDs in SpA patients and their possible association with main disease outcome such as disability and comorbidities. Further, we sought to investigate potential gender and age differences in MNDs and SpA association.

Patients and Methods

A total of 220 consecutive patients with diagnosis of SpA attending the SpA outpatients Clinic at Rheumatology Units of "Tor Vergata" University Hospital (Rome), and "Federico II" University Hospital (Naples), were included in the study (time-frame Sept 2020-Dec 2020).

Inclusion criteria were: (a) age ≥18 and ≤80 years; (b) diagnosis of SpA, including Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), enteropathic SpA (ESpA), Behçet disease (BD), in accordance with the international criteria[25-31]. Exclusion criteria consisted of: haemoglobinopathies; abnormal parathyroid function; pregnancy or lactation; kidney and/or liver failure; respiratory and/or heart failure; alcohol abuse; neoplasia; ongoing vitamins and/or folate and/or iron supplementations and/or treatments with bisphosphonates and/or denosumab.

At the enrollment, data on age, gender, SpA disease duration, comorbidities (including metabolic and autoimmune disorders), occurrence of extra-articular manifestations [PsO and other skin (erythema nodosum, pyoderma gangrenosum), eye (uveitis, iridocyclitis, episcleritis), IBD, and sclerosing cholangitis], concomitant treatments including selective COX-2 inhibitors (COXIBs), conventional synthetic and biologic disease modifying antirheumatic drugs (cs- and b-DMARDs), were recorded. Composite disease severity scores were used to assess SpA disease activity: Disease Activity Index for PsA [(DAPSA) 0-4 remission, 5-14 low, 15-28 moderate, >28 high disease activity][32], and Ankylosing Spondylitis Disease Activity Score [(ASDAS, C Reactive Protein-based) <1.3 inactive disease, 1.3-2.0 low, 2.1-3.5 high, and >3.5 very high disease activity][33], as appropriate. The Health Assessment Questionnaire modified for SpA (HAQ-S) was also registered from all the patients[34].

All the enrolled patients underwent blood chemistry analysis to determine C-reactive protein (CRP, mg/L), serum uric acid (SUA), triglycerides (TG), glucose (Gly), 25(OH)D, B12, FA, and ferritin (Fe) that were determined using routine laboratory techniques. Metabolic abnormalities included obesity defined BMI ≥ 30[35].

25(OH)D status was classified as deficiency when it was below 20 ng/ml while B12 deficiency was defined when it was below 200 pg/mL. FA value ≤ 4 ng/mL was considered as deficiency, serum Fe levels ≤ 15 ng/dL were considered as an iron deficiency. Anemia was defined with Hb ≤ 12 g/dl[10,36-38].

The study was approved by the independent ethics committee from "Tor Vergata" University of Rome. Informed consent was obtained from all patients before they were included in the study. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and was consistent with good clinical practice guidelines.

Statistical Analysis

Mean and standard deviation (SD) express normally distributed variables; for non-symmetric distributed data, median and range were used. Continuous variables were compared by using either the parametric unpaired T test or the non-parametric Mann-Whitney U test, as appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the Chi-squared test or Fisher's exact test, as appropriate. Pearson's r measured the strength of the relationship between two variables. Multivariate analyses were used to evaluate the association between multiple variables. The *p*-values <0.05 were considered significant. All statistical analyses were performed using the GraphPad Prism version 9 (GraphPad software, La Jolla, CA, USA).

Results

Characteristics of Study Population

The study cohort involved an equal proportion of PsA (n=110) and non-psoriatic SpA (n=110) which included peripheral SpA (n=57, 51.8%), axial SpA (n=47, 42.7%), and SpA associated to BD (n=6, 5.5%). In the entire cohort, male (n=83) and female (n=137) patients were age-matched and similar for diagnosis, disease duration and activity, and concomitant treatments (Table I). Univariate analysis documented that males had higher mean SUA (p<0.0001) and Gly

Table I. Characteristic of the study population according to the gender difference.

	Females (N=137)	Males (N=83)	*p*
Age (yrs)	51.65 ± 13	52.9 ± 12.8	ns
BMI	24 (17.2-50.2)	25.8 (19.6- 43.6)	0.03
CRP (mg/L)	2.9 (0-53)	2 (0-61)	ns
Gly (mg/dl)	86 (66-134)	90 (71-166)	0.03
SUA (mg/dl)	4.1 (0.7-8.5)	5.3 (2.5-10.6)	< 0.0001
TG (mg/dl)	112 (35-291)	82 (0.6-349)	0.008
Hb (mg/dl)	13 ± 1.2	14.4 ± 1.4	ns
Fe (mg/L)	37 (2-148)	64 (4-452)	0.03
25(OH)D (ng/ml)	28.2 (5-67)	25 (5-50)	0.02
B12 (pmol/L)	350 (60-990)	313 (47-797)	ns
FA (ng/ml)	7 (1.7-40)	6.9 (1.8-39)	ns
PsA (N/%)	73/68.23	34/31.77	ns
SpA (N/%)	64/41	49/59	ns
Concomitant IBD (N/%)	56/65.9	29/34.1	ns
D.D. (months)	69 (6-540)	76.5 (3-768)	ns
Remission/LDA (N/%)	62/45.25	47/56.6	ns
Moderate-high D.A. (N/%)	75/54.75	36/43.4	ns
HAQ-S	1 (0-2.4)	0.3 (0-1.9)	0.03
COXIBs (N/%)	21/15.4	8/9.6	ns
cDMARDs monotherapy (N/%)	35/25.5	10/12.1	ns
bDMARDs (N/%)	81/59.12	65/78.4	ns

BMI, body mass index; CRP, C-reactive protein; Gly, glycemia; SUA, serum uric acid; TG, triglycerides; Hb, haemoglobin; Fe, ferritin; 25(OH)D, vitamin D; B12, vitamin B12; FA, folic acid; PsA, psoriatic arthritis; SpA, spondyloarthritis; IBD, inflammatory bowel disease; D.D., disease duration; LDA, low disease activity; HAQ-S, Health Assessment Questionnaire modified for SpA; COXIBs, selective COX-2 inhibitors; cDMARDs, conventional Disease Modifying Antirheumatic drugs; bDMARDs, biological Disease Modifying Antirheumatic drugs. Mean ± standard deviation express normally distributed variables; for non-symmetric distributed data, median and range were used. Continuous variables were compared using the parametric unpaired T test or the nonparametric Mann–Whitney U test, when appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the Chi-squared test or Fisher's exact test, when appropriate. The *p*-values < 0.05 were considered significant.

levels (p=0.03) than females. Inversely, when compared to males, females showed higher TG levels (p=0.008). In males, median BMI was higher than in females (p=0.03) and positively correlated with age (p=0.01). Interestingly, just in female patients, BMI directly correlated with HAQ-S (p=0.03).

MNDs in Study Population

Anemia occurred in 13.6% of the study cohort: females had a higher prevalence of anemia than males (p=0.004, O.R. 5.3, C.I.95% 1.7-17; Figure 1A). In addition, females showed a higher iron deficiency than males (p=0.02, O.R. 5.4, C.I.95% 1.4-24; Figure 1A), as well as lower mean Fe levels (p=0.0003) (Table I). Accordingly, using multivariate analysis, Hb revealed significant inverse correlations with age (p=0.01), and CRP (p=0.008), only in males.

We found hypovitaminosis D in 23.2% of the whole cohort, without gender difference in the prevalence of the 25(OH)D deficiency (Figure 1A). However, in male patients, mean 25(OH)D levels were lower than in females (p=0.02), and inversely correlated with disease duration (p=0.02).

Deficiencies of serum B12 and FA occurred in 13.2% and 22% of the whole cohort, respectively. FA deficiency was associated with low serum B12 levels in 31% of cases, with almost similar occurrence in males and females (Figure 1A).

SpA patients were also stratified in accordance with disease activity to analyze potential differences in MNDs. In our cohort, 106 patients were in remission/LDA while 114 were in moderate/high disease activity (Table II), with a higher prevalence of female sex within the second group (p=0.05). When compared with patients in remission/LDA, patients in moderate/high SpA disease activity had higher BMI (p=0.04), and HAQ-S (p<0.0001), as well as lower Hb (p=0.02), and Fe (p=0.03) levels (Table II). A lower SpA disease duration (p=0.03) and a higher prevalence of concomitant IBD resulted among patients in moderate/high disease activity (p=0.001, O.R. 0.4, 95%C.I. 0.2-0.7). When compared with patients on remission/LDA, no difference in prevalence of patients with single micronutrient deficiency was evident (Figure 1B).

MNDs in Accordance with Extra-Articular Involvement

In patients with extra-articular manifestations (n=151), female sex was prevalent with F:M ratio = 2; instead in patients without extra-articu-

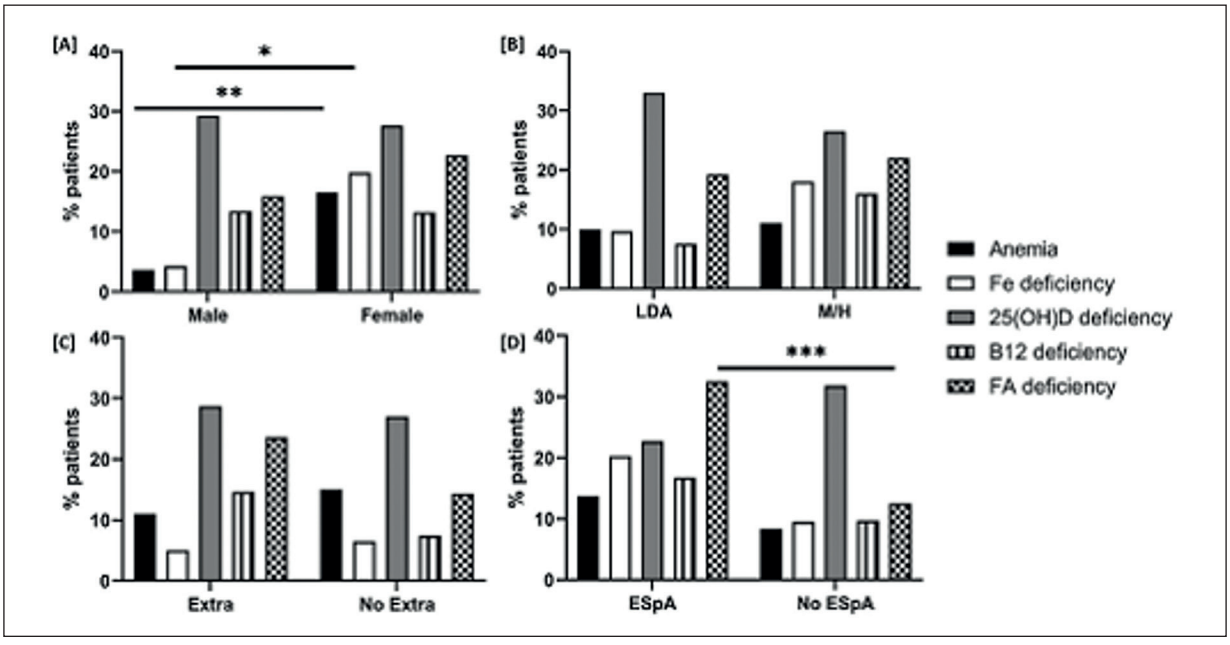

Figure 1. Analysis of micronutrients deficiencies distribution in the study population. Anemia was defined as Hb (hemoglobin)≤ 12 g/dl; Fe (ferritin) deficiency as Fe ≤15 ng/dL; 25(OH)D (vitamin D) deficiency as 25(OH)D ≤20 ng/ml; B12 (vitamin B12) as B12 ≤200 pg/mL; FA (folic acid) as FA≤4 ng/mL; LDA, low disease activity; M/H, moderate-high disease activity; Extra, with extra-articular involvement; No Extra, without extra-articular involvement; ESpA, enteropathic spondyloarthritis. Groups were compared using the Chi-squared test or Fisher's exact test, when appropriate. The p-values <0.05 were considered significant. (*p<0.05; **p<0.01; ***p<0.001).

Table II. Data from the study population according to disease activity.

	Remission/LDA (n=106)	Moderate/High (n=114)	p
Gender (F/M)	59/47	78/36	0.05
Age (yrs)	51±13.7	53±12	ns
BMI	24 (17.6-50.2)	25.4 (17.2-43.6)	0.04
CRP (mg/l)	1.4 (0-28)	3.7 (0-61)	ns
Gly (mg/dl)	85 (68-134)	88.5 (66-166)	ns
SUA (mg/dl)	4.7±1.4	4.7±1.5	ns
TG (mg/dl)	111 (35-310)	108 (33-349)	ns
Hb (g/dl)	13.8±1.4	13.4±1.4	0.02
Fe (mg/l)	61 (4-452)	39 (2-396)	0.03
25(OH)D (ng/ml)	26.9±10.9	27.1±10.8	ns
B12 (pmol/L)	362.5±136.1	377±180	ns
FA (ng/ml)	7.5 (1.8-40)	6.6 (1.7-37)	ns
Extra-articular (N/%)	67/63.2	84/73.7	ns
Concomitant IBD (N/%)	29/27.3	56/49.1	0.001
D.D. (months)	84 (12-768)	60 (0-480)	0.03
HAQ-S	0.3 (0-2)	1.2 (0-2.8)	< 0.0001
COXIBs (N/%)	15/14.1	15/13.1	ns
cDMARDs monotherapy (N/%)	23/21.7	21/18.4	ns
bDMARDs (N/%)	68/64.1	78/68.4	ns

LDA, low disease activity; BMI, body mass index; CRP, C-reactive protein; Gly, glycemia; SUA, serum uric acid; TG, triglycerides; Hb, haemoglobin; Fe, ferritin; 25(OH)D, vitamin D; B12, vitamin B12; FA, folic acid; IBD, inflammatory bowel disease; D.D., disease duration; HAQ-S, Health Assessment Questionnaire modified for SpA; COXIB, selective COX-2 inhibitors; cDMARDs, conventional Disease Modifying Antirheumatic drugs; bDMARDs, biological Disease Modifying Antirheumatic drugs. Mean ± standard deviation expresses normally distributed variables; for non-symmetric distributed data, median and range were used. Continuous variables were compared using the parametric unpaired T test or the nonparametric Mann-Whitney U test, when appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the Chi-squared test or Fisher's exact test, when appropriate. The *p*-values <0.05 were considered significant.

lar manifestations (n=69), the F:M ratio was 1 (p=0.03, Table III). No difference in distribution of diagnosis as well as in disease duration, disease activity, and concomitant treatments occurred between groups.

Obesity was more frequent in patients without extra-articular manifestations than in patients with it (30.7% *vs.* 13.9%, p=0.02, O.R. 0.36, 95% 0.25-0.82). Accordingly, in patients without extra-articular involvement, BMI and HAQ-S were higher than in patients with extra-articular involvement (p=0.036, and p=0.01, respectively), and were positively correlated (r –0.5, p=0.006); in addition, HAQ-S showed an inverse correlation with Hb (r –0.5, p<0.0001).

Serum levels of 25(OH)D were lower in patients without extra-articular involvement (p=0.04) while serum levels of B12 were lower in patient with extra-articular manifestations (p=0.005) (Table III). Interestingly, in SpA patients without extra-articular involvement, disease duration inversely correlated with Fe serum levels (r –0.67, p<0.0001).

Anemia and Fe, 25(OH)D, B12, and FA deficiency showed a similar distribution between SpA patients with extra-articular manifestations and without it (Figure 1C).

ESpA occurred in patients with concomitant Chron's disease (n=62) and Ulcerative Colitis (n=23): at the evaluation, all the ESpA patients (n=85) were on clinical remission for IBD.

When comparing patients with and without IBD, no difference in age and gender distribution as well as metabolic abnormalities occurred, except for BMI that resulted higher in patients without IBD (p=0.03) (Table IV). On the other hand, ESpA patients had a shorter SpA disease duration (p=0.004) and a higher prevalence of moderate/high disease activity (p=0.02, O.R. 1.95, 95%C.I. 1.13-3.4), a higher HAQ-S (p<0.0001), and a grater COXIB-use (p=0.02, O.R. 2.5, 95%C.I. 1.2-5) when compared with SpA patients without IBD (Table IV). Interestingly, 25(OH)D serum levels were lower in SpA patients without IBD than in ESpA (p=0.04) (Table IV). Prevalence of patients with FA deficiency was higher in ESpA than in SpA patients without IBD (p=0.002, O.R. 3.3, 95%C.I. 1.5-6.8; Figure 1D). According to multivariate analyses, HAQ-S positively correlated with BMI (p=0.01) in SpA patients without IBD;

Table III. Data from the study population according to extra-articular involvement.

	Extra-articular (n= 151)	Non-extra-articular (n= 69)	p
Gender (F/M)	101/50	36/33	0.03
Age (yrs)	51.9 ± 12.8	52.5 ± 13.2	ns
BMI	24 (17.2-43.6)	26.4 (20-50.2)	0.03
CRP (mg/l)	2 (0-61)	3 (0-37)	ns
Gly (mg/dl)	87 (66-134)	87 (68-166)	ns
SUA (mg/dl)	4.72±1.5	4.8±1.3	ns
TG (mg/dl)	121.1±61.1	120±54	ns
Hb (g/dl)	13.5±1.3	13.9±1.5	ns
Fe (mg/l)	45.5 (2-262)	48 (5-452)	ns
25(OH)D (ng/ml)	28.1±11.6	24.8±8.5	0.04
B12 (pmol/L)	331.5±130	386±130	0.005
FA (ng/ml)	7.4 (1.7-40)	6.6 (2.9-20)	ns
D.D. (months)	70 (0-540)	84 (3-768)	ns
Remission/LDA (N/%)	67/ 44.3	39/57	ns
Moderate/high D.A. (N/%)	82/54.3	29/42	ns
HAQ-S	0.68±0.74	1±0.7	0.01
COXIBs (N/%)	22/14.5	8/5.3	ns
cDMARDs monotherapy (N/%)	31/20.5	13/18.8	ns
bDMARDs (N/%)	98/64.9	48/69.5	ns

BMI, body mass index; CRP, C-reactive protein; Gly, glycemia; SUA, serum uric acid; TG, triglycerides; Hb, hemoglobin; Fe, ferritin; 25(OH)D, vitamin D; B12, vitamin B12; FA, folic acid; D.D., disease duration; LDA, low disease activity; HAQ-S, Health Assessment Questionnaire modified for SpA; COXIB, selective COX-2 inhibitors; cDMARDs, conventional Disease Modifying Antirheumatic drugs; bDMARDs, biological Disease Modifying Antirheumatic drugs. Mean ± standard deviation expresses normally distributed variables; for non-symmetric distributed data, median and range were used. Continuous variables were compared using the parametric unpaired T test or the nonparametric Mann–Whitney U test, when appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the Chi-squared test or Fisher's exact test, when appropriate. The *p*-values <0.05 were considered significant.

in addition, B12 was inversely related with CRP (p=0.006) while being directly related with FA (p=0.03).

Discussion

The status of malnutrition has long been known as globally "immune suppressive" as well as overnutrition has been shown to promote inflammation[39,40]. Evidence[41] in literature reporting that inflammatory cytokines are induced in obese adipose tissues and that these cytokines lead to metabolic diseases illustrate a strong link between metabolism and immunological state. In patients with inflammatory arthritis as SpA, inflammatory-dependent dysmetabolism has been described. In this context we explored, for the first time, the status of several micronutrients, reporting a relevant prevalence of MNDs independently from SpA phenotype. Percentages of patients with defined MNDs were not different between SpA with and SpA without extra-articular involvement including PsO and/or IBD. Furthermore, our analysis evidenced a complex interplay of age, gender, and metabolic status with MNDs in SpA patients. In our study population, gender was equally distributed without difference in disease diagnosis and activity. However, in line with other studies, female gender resulted prevalent among SpA patients with extra-articular involvement. This is in accordance with the idea that different manifestations of disease might be linked to immunological, hormonal, and genetic predisposition in female[42,43]. Conversely, metabolic abnormalities occurred in male subjects in terms of SUA, glycemia, and BMI with respect to females, supporting the possible role of gender in influencing metabolic expression in SpA. Intriguingly, just in males, BMI showed a direct linear correlation with age, whilst in females BMI correlated manly with disability. Data from literature reported a direct correlation among BMI and age, disease progression, and poorer patient outcomes, suggesting that chronic inflammatory state underlying obesity could support the production of pro-inflammatory cytokines independently of SpA activity[44]. Recently other studies[45] documented an association between SpA activity and BMI in male patients. Our findings

Table IV. Data from the study population according to the presence of concomitant inflammatory bowel disease.

	ESpA (n=85)	No-ESpA (n=135)	*p*
Gender (F/M)	56/29	80/55	ns
Age (yrs)	50.9 ± 13.1	52.81 ± 12.9	ns
BMI	23.6 (17.2-37.3)	25.78 (17.26-50.2)	0.03
CRP (mg/L)	2.9 (0-61)	2 (0-37)	ns
Gly (mg/dL)	86 (70-134)	87 (66-166)	ns
SUA (mg/dL)	4.5 (1.7-8.7)	4.5 (0.7-10.6)	ns
TG (mg/dL)	101 (45-297)	112 (33-349)	ns
Hb (g/dL)	13.5 ± 1.3	13.7 ± 1.5	ns
Fe (mg/L)	47.5 (2-211)	45.5 (3-452)	ns
25(OH)D (ng/mL)	29 (7-65)	26.2 (5-67)	0.04
B12 (pmol/L)	332 (47-997)	349 (60 – 726)	ns
FA (ng/mL)	6.7 (1.7-40)	7.1 (2.7-39)	ns
D.D. (months)	57 (0-504)	84 (3-768)	0.004
Remission/LDA (N/%)	31/36.4	78 / 57.8	< 0.002
Moderate/ High D.A. (N/%)	50/58.8	57 / 42.2	0.02
HAQ-S	0.51 ± 0.53	0.93 ± 0.7	< 0.0001
COXIBs (N/%)	19/22.35	14/10.4	0.02
cDMARDs monotherapy (N/%)	16/18.8	24/17.8	ns
bDMARDs (N/%)	50/58.8	97/71.8	ns

BMI, body mass index; CRP, C-reactive protein; Gly, glycemia; SUA, serum uric acid; TG, triglycerides; Hb, hemoglobin; Fe, ferritin; 25(OH)D, vitamin D; B12, vitamin B12; FA, folic acid; D.D., disease duration; LDA, low disease activity; HAQ-S, Health Assessment Questionnaire modified for SpA; COXIB, selective COX-2 inhibitors; cDMARDs, conventional Disease Modifying Antirheumatic drugs; bDMARDs, biological Disease Modifying Antirheumatic drugs. Mean ± standard deviation expresses normally distributed variables; for non-symmetric distributed data, median and range were used. Continuous variables were compared using the parametric unpaired T test or the nonparametric Mann–Whitney U test, when appropriate. Categorical variables were presented with absolute frequencies and percentages and were compared using the Chi-squared test or Fisher's exact test, when appropriate. The *p*-values <0.05 were considered significant.

showed that, independently of SpA group, the most frequent metabolic abnormality was obesity that occurred in above 20% of the population. Furthermore, obesity was twice more frequent in SpA patients without extra-articular manifestations than in patients with it, in accordance with previous observational cohort studies, in which obesity frequently occurred in SpA, often in association with other metabolic abnormalities, age, and a worse clinical outcome[46-49]. Moreover, obesity is an "inflammatory disorder", with impaired immune functions frequently caused or accompanied by alterations in gut microbiota independently of the occurrence of overt IBD[50].

As expected, in our study cohort, both anemia and iron deficiency were significantly prevalent in female patients[51]. As known, women, particularly in reproductive age, are at higher risk of iron deficiency, mainly due to physiological loss and pregnancy[52]. Furthermore, in this context, an elevated frequency of anemia resulted in the whole SpA cohort without difference related to extra-articular involvement. So far, few studies[53] focused on prevalence of anemia in SpA cohorts, reporting a relatively elevated prevalence in SpA patients often in association with iron deficiency. In our study cohort, male gender was associated with significant correlations between anemia and age of patients as well as CRP levels, as described in other chronic diseases[51]. Anemia can be common in patients with SpA and RA because of the pathogenetic role of many pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα), and interleukin-6 (IL-6), through different mechanisms. Therefore, findings highlighting anemia and its correlation with disease activity could be explained by the chronic inflammatory status occurring in severe SpA patients[54-56].

In the entire cohort study, we found a high prevalence of 25(OH)D deficiency, according to previous evidence of 25(OH)D deficiency as a frequent condition in SpA patients, also associated with a long disease duration[57-60]. In this context, we interestingly documented that in males, mean 25(OH)D serum levels were lower than in females and also inversely correlated with disease duration. Other authors reported 25(OH)D deficiency in older men, especially if obese and sedentary: however, a defined gender difference of 25(OH)D deficiency in SpA is yet to be re-

ported[61]. This could be due to a stricter 25(OH)D observation adopted in the female cohort in order to prevent possible diseases with relevance for 25(OH)D occurring in postmenopausal women[62]. Hence, our study suggests the need to focus attention on supplementing 25(OH)D in SpA patients mainly in elderly men.

In the whole study population, B12 deficiency was not frequent, but deficit of FA resulted relevant and often associated with B12 deficiency, with almost similar occurrence in males and females. We verified lower B12 levels in patients with extra-articular manifestations, probably related to concomitant gastro-intestinal manifestations. In this context, when compared with SpA patients without IBD, ESpA patients showed a significantly higher prevalence of FA deficiency. Interestingly, B12 levels directly correlated with FA, even in the absence of a concomitant IBD. Of note, the occurrence of IBD was significantly associated with a moderate/high disease activity status, as well as a greater exposition to COX-IBs[63]. Despite this evidence highlighting the role of concomitant IBD on SpA disease activity, patients without gastro-intestinal involvement had higher BMI, HAQ-S, and lower mean 25(OH) D. These findings suggest a strong association among metabolic abnormalities (obesity), MNDs, and disability in SpA, regardless of intestinal diseases and support regulatory role of nutritional components in the gut microbiota and immune system interplay. In line with that observation, SpA patients on moderate/high disease activity had higher BMI and HAQ-S than patients on remission/LDA, in association with lower levels of Fe and Hb. These results are in accordance with several studies[44,64] showing associations between an overweight/obese BMI and a high disease activity. In particular, a recent metanalysis[65] showed that overweight and obese SpA patients have a tendency to show higher disease activity scores when compared to normal-BMI patients. This difference seems to be clinically significant concerning the comparison between obese and normal BMI patients, and more for Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Study limitations consist of cross-sectional study design, relatively

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

PT, FC, and MSC contributed to the conceptualization and scope. PT, FC, and DMD outline of this paper. ADA, SF, MF, LC and MT collected and analyzed data. PT, PC, MSC, DMD, AB, and FC participated in preparing the manuscript, read, and approved the final version.

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