



Nutritional profile of patients with chronic inflammatory diseases in the age of biologicals

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Abstract

Tumor necrosis factor alpha (TNF α) has an important role in the body composition of patients with rheumatoid arthritis (RA), Crohn's disease (CD), and spondyloarthritis (SpA). We aimed to assess the nutritional profile of patients with RA, CD, and SpA undergoing remission with multiple therapies comparing to controls and to analyze the effect of anti-TNF α medications in the nutritional parameters of these patients. One hundred thirty-one patients were included: 44 with RA, 43 with CD, and 44 with SpA. Patients receiving anti-TNF α were compared with those receiving non-biologic treatment as well as to controls. Nutritional profile included body mass index (BMI), waist circumference (WC), mid-upper arm circumference, and triceps skinfold measurement. Overweight and obesity were highly prevalent on three assessed groups. In patients with RA, BMI was >25 kg/m² in 74.9% patients and 49.2% controls ($p < 0.0005$); in CD, in 55.7% patients and 41.2% controls ($p < 0.0001$); and in SpA, in 68.1% patients and 43.5% controls ($p < 0.0001$). Central obesity was higher in all three disease groups when compared to healthy controls. There was no significant difference on nutritional parameters in patients using or not using anti-TNF α medications, except in patients with SpA, in which biologic therapy was significantly associated with lower BMI and WC, when compared to other therapies. Overweight, obesity, and elevated WC were more prevalent in patients with RA, CD, and SpA undergoing remission when compared to controls despite of used therapy. The use of biologic drugs in patients with SpA was associated with a lower BMI and lower WC.

Keywords Biologic therapy · Chronic inflammatory diseases · Crohn's disease · Nutritional profile · Rheumatoid arthritis

Introduction

The chronic inflammatory process that underlies the pathophysiological process of diseases such as rheumatoid arthritis

(RA), Crohn's disease (CD), and spondyloarthritis (SpA) is recognized as an important determinant in the patient's body composition. Malnutrition, loss of muscle mass, and cachexia usually reflect the nutritional profile of those they affect [1, 2].

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The etiology of malnutrition associated with chronic inflammatory diseases is multifactorial [2]. In RA and SpA patients, it may occur due to loss of appetite secondary to disease activity and to gastrointestinal intolerance to medications used in the treatment or, yet, to muscle atrophy brought by immobility secondary to the physical limitations imposed by the rheumatic disease [3]. In patients with CD, malnutrition may be justified by a reduced appetite and malabsorption due either to disease activity or intestinal resections [2]. In addition, pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF α (tumor necrosis factor alpha) are able to yield important changes in the body composition and nutritional profile [4]. IL-1 and TNF α are both associated with increased catabolism, while IL-1 is implicated in the appearance of anorexia [4]. Therefore, nutritional status improvement in such patients depends on the control of the chronic inflammatory process, which can be reached nowadays with the use of biological drugs. Among them, the use of anti-TNF α drugs is emphasized [1, 5]. However, if on the one hand such drugs may avoid the catabolic state associated with uncontrolled inflammation, on the other, they may allow the appearance of overweight and obesity. This risk is increased when they are combined with the use of glucocorticoids, inappropriate diet, and sedentary behavior. Although the correction of weight loss is desirable, oscillation of body mass index (BMI) to the other extreme is also not adequate, especially when it happens at the expense of higher proportion of fat, without the corresponding increase in muscle mass. Some authors have warned against the risk of the so-called sarcopenic obesity, a term coined to describe the imbalance between muscle mass and body fat that contributes to increased risk of cardiovascular disorders and decreased survival [6].

Despite the widespread use of anti-TNF α therapy and recognition of the positive results in the management of chronic inflammatory diseases, there are few inquiries that explore its influence on the patients' nutritional status. The aim of this study was to evaluate the nutritional status of patients with RA, CD, and SpA in the remission phase (under biological therapy or immunosuppressive drugs), comparing them with healthy controls.

Methods

This is a cross-sectional study conducted in two reference hospitals—Clinical Hospital, Federal University of Paraná, and Evangelical Hospital of Curitiba, approved by the local Committee of Ethics in Research.

We included 131 patients with chronic inflammatory diseases, divided into three categories:

Group A: 44 patients with RA, diagnosed by American College of Rheumatology classification criteria

[7], of which 21 (47.7%) were using biological therapy; 23 were on immunosuppressive medications.

Group B: 44 patients with SPA as diagnosed according to Assessment of SpondyloArthritis International Society (ASAS) criteria [8]; 23 patients (52.3%) were on biological treatment and 21 patients were on immunosuppressive medications

Group C: 43 patients with CD as diagnosed by endoscopic finding or imaging studies [9], 20 (46.5%) on biological therapy and 23 patients on immunosuppressive medications.

This is a convenience sample that included individuals according to appointment order for regular consultations. All participants signed consent and were over 18 years of age. Patients on anti-TNF α drugs should be on this treatment for more than 6 months. Patients with active disease, history of intestinal resections, and use of nutritional supplementation were excluded.

Each group had its nutritional status compared with controls paired for gender and age. In addition, each group was individually studied to analyze the influence of anti-TNF α therapy on the nutritional profile. The control group was obtained from ophthalmology and otorhinolaryngology outpatient units and was composed of individuals who did not have any chronic inflammatory disease.

Epidemiological and clinical data were collected through direct questioning and included information on age, gender, ethnic background, tobacco and alcohol exposure, and used medications. Inflammatory disease activity was measured by the following instruments: DAS (Disease Activity Score)-28 ESR (erythrocyte sedimentations rate) for RA [10]; Harvey-Bradshaw index for CD [11]; BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) for SpA [9] DAS-28-ESR is an instrument that scores the number of inflamed and painful joints of a patient with RA, their general health condition, and the ESR. Values below 3.2 are considered as mild disease activity [10]. The Harvey-Bradshaw index takes into account patient's general condition and abdominal and extra intestinal clinical symptoms of a patient with CD; values less than 5 indicates remission of the disease [11]. BASDAI scores pain and stiffness in the axial, peripheral joints and entheses of a patient with SpA; a value less than 4 is considered as inactive disease [9]. In addition, for all patients, we measured the CRP (C-reactive protein) serum levels by immunonephelometry.

The anthropometric evaluations were performed by a single nutritionist in the period before consultation: body weight, height; waist circumference (WC), upper mid arm circumference (MUAC), and tricipital skin fold measurement (TSM) were measured. Weight measurement was performed by a Marte® portable digital scale and the height was measured

using a Cardiomed® transportable stadiometer of anodized aluminum. BMI was calculated dividing weight in kilograms, by squared height in meters. The values adopted for statistical analysis were as follows: BMI < 18 kg/m² as low weight; between 18 and 24.9 kg/m² as eutrophic weight; between 25 and 30.9 kg/m² as overweight; and > 30.9 kg/m² as obesity [12]. MUAC and WC were performed according to the technique described by Cuppari [13] using an inelastic anthropometric tape. The TCF was measured using a Cescorf® plicometer according to a Cuppari-standard technique [13]. Arm muscle circumference (AMC) was calculated using the following formula: (MUAC-TSM) × 0.314. Values of CMB < 15 cm were considered low [14].

Data distribution was studied by the Kolmogorov-Smirnov test. Central tendency were expressed as mean and standard deviation (SD) when the sample was parametric and median and interquartile (IQR) if non-parametric. Fisher's and chi-square tests were used for nominal data association studies. Mann-Whitney tests (non-parametric data) and unpaired *t* tests (parametric data) were used for numerical data associations. Data were calculated using Graph Pad Prism software version 5.0. The relevance adopted of was 5%.

Results

RA group

The description of the RA sample is in Table 1. The control group of this sample had 79 patients: 60/79 (75.9%) females (with $p = 0.64$ for gender pairing) and mean age of 52.65 ± 13.42 (with $p = 0.35$ for age pairing).

Comparison of RA group with controls showed results in Table 2, where it is possible to see that RA patients had a trend to be more overweight and obese and had higher WC and lower TSM than controls. The comparison of BMI expressed in categories was higher in RA patients ($p = 0.0005$) than controls and the RA patient's AMC was low in 31.8% of them while controls had this value within normality ($p < 0.0001$). Table 2 shows also the comparison of RA patients using and not using anti-TNF drugs. The only difference noted was in waist circumference.

Oral glucocorticoid was used in 61.9% of RA patients on anti-TNF drugs and in 65.2% of those using only traditional disease-modifying agents.

SpA group

SpA sample characteristics are in Table 1. The control group for the SpA sample was 62 patients: 40/63 (66.6% males; with $p = 0.10$ for gender) and mean age was 49.3 ± 17.3 years ($p = 0.78$ pairing for age).

The comparison of SpA patients and controls is in Table 3 where it is noted that SpA patients had higher BMI and WC and lower TSM than controls. BMI was also higher in SpA patients when expressed in categories ($p = 0.0001$). Table 3 also shows the comparison between users and non-users of anti-TNF drugs. The anti-TNF users had lower BMI, TSM, and WC.

CD group

CD group characteristics are in Table 4. The control group for this sample was 63 individuals: 40/63 (63.4%) were females (with $p = 0.13$ in the pairing for gender) and the mean age was 44.3 ± 12.41 years (pairing for age with $p = 0.73$).

When the CD group and controls were compared, it was found that BMI, WC, and AMC were higher and TSM was lower in CD patients than controls as seen in Table 4. Overweight and obesity were found in 55.7% of CD patients versus 41.2% of controls ($p < 0.0001$).

It was not possible to show any difference in the studied nutritional parameters when the comparison of CD patients with and without anti-TNF was done (all $p = ns$).

Discussion

The results of the present study showed that overweight and obesity, higher WC, and lower TSM are more common in RA, CD, and SpA patients with low inflammatory activity than in controls. These findings highlight that in patients with these chronic diseases, there is increased body fat including central obesity. Using anti-TNF α did not impact these findings in RA and CD groups. Only SpA patients had significant reduction in BMI, WC, and TSM under anti-TNF α treatment.

High prevalence of obesity in RA has already been found by others. An English study [6] found obesity in 31% of RA patients. Similarly, another multicentric study showed a prevalence of obesity in 18% of such patients [15]. Both, like the current study, reinforce the finding of an increase in the BMI of RA patients in apparently good control of their disease. In addition, it is important to note that this increase in BMI is mainly due to the increase of fat, in disadvantage of muscle mass, as demonstrated by an increase in the WC and lower AMC. Higher body fat mass has been identified in RA patients from Mexico in a study bioelectrical impedance analysis (BIA) and including dietary pattern evaluation [16]. Several factors contribute to this nutritional profile in this context. The main ones are the reduction of physical activity by the joint limitation imposed by rheumatic disease and the use of glucocorticoids, which increase the appetite, alter the mobilization of lipids, and cause neolipogenesis and adipogenesis [17]. It is worth mentioning the influence of overweight in the morbidity

Table 1 Demographical and clinical data of studied groups of patients

	Rheumatoid arthritis (<i>n</i> = 44)	Spondyloarthritis (<i>n</i> = 44)	Crohn's disease (<i>n</i> = 43)
Females	39/44 (79.5%)	23/44 (52.2%)	22/43 (51.1%)
Mean age—years (range)	54.8 ± 11.10 (28–81 years)	50.2 ± 13.55 (20–78 years)	45.4 ± 12.41 (18–70 years)
Ethnic background (autodeclared)	Caucasian 75% Afrodescendents 25%	Caucasian 84% Afrodescendents 16%	Caucasian 75% Afrodescendents 25%
Tobacco use	9/44 (20.5%)	6/44 (13.7%)	3/43 (6.9%)
CRP median interquartile range (IQR)	12.0 mg/dL (IQR = 6.0–15.0 mg/dL)	8.5 mg/dL (IQR = 4.7–23.5 mg/dL)	0.43 mg/dL (IQR = 0.24–1.03 mg/dL)
Anti-TNF α drugs	21/44 (47.7%) Infliximab—56.5% Etanercept—43.5%	23/44 (52.3%) Infliximab—17.3% Etanercept—60.8% Adalimumab—1.7%	20/43 (46.5%) Infliximab—78.2% Adalimumab—11.5%
Treatment duration with anti-TNF drugs (range)—months	48 (12–84)	33 (8–90)	36 (6–108)
DMARDs	23/44 (52.3%) Methotrexate 61.3% Leflunomide 43.1% Antimalarial 20.4%	21/44 (41.7%) Methotrexate 22.7% Sulphasalazina 4.5% AINES 11.3%	23/43 (53.5%) Methotrexate 16.6% Azathioprine 54.7%
Oral glucocorticoids	29/44 (65.9%)	6/44 (13.6%)	37/43 (86%)
Score activity	DAS 28-ESR median 2.2 ± 1.0 (range 1.2–3.1)	BASDAI median 2.5 (range 1.0–4.2)	Harvey-Bradshaw index median 3.0 (IQR = 2.0–4.0)
Prevalence of diabetes mellitus	5/44 (11.3%)	1/44 (2.2%)	5/43 (11.6%)
Prevalence of arterial hypertension	15/44 (34.0%)	13/44 (29.5%)	6/43 (13.9%)

CRP C-reactive protein, DAS Disease Activity Score-28, ESR erythrocyte sedimentations rate, BASDAI Bath Ankylosing Spondylitis Disease Activity Index, AINEs anti-inflammatory non-steroidal drugs

and mortality of individuals with RA due to mechanical joint overload and by aggravating cardiovascular risk. Cardiovascular risk is already increased by the RA inflammatory process itself in these patients [6, 15]. Regarding the possible role of anti-TNF α in the change of body composition, the findings of the present analysis are in agreement with those of Serelis et al. [2] that studying 19 patients with

RA failed to demonstrate any modification in body composition after one year of treatment with this drug. In contrast, Engvall et al. [1] observed an important increase of fat with preservation of muscle mass in RA patients using infliximab, an effect they did not observe with the use of habitual disease-modifying drugs, despite of similar control of disease inflammatory activity.

Table 2 Study of anthropometric parameters of patients with rheumatoid arthritis (RA). Comparison with controls and study of anti-TNF α treatment influence

Comparison of RA patients with controls			
Variable	Total RA patients (<i>n</i> = 44)	Control group (<i>n</i> = 79)	<i>p</i>
Body mass index—kg/m ² (median)	27.1 (24.25–30.53)	25.0 (22.89–28.16)	0.08
Tricipital skin folder—mm (median)	16.0 (13.2–21.7)	27.0 (21.0–33.0)	< 0.0001
Arm muscle circumference—cm (median)	23.4 (18.8–25.9)	21.8 (19.3–25.3)	0.57
Waist circumference—cm (mean)	97.1 ± 13.4	91.6 ± 15.5	0.01
Comparison of RA patients treated with and without anti-TNF			
	RA with anti-TNF (<i>n</i> = 21)	RA without anti-TNF (<i>n</i> = 23)	<i>p</i>
Body mass index (median)—kg/m ²	28.1 (24.8–30.8)	26.7(23.1–30.3)	0.33
Tricipital skin folder (median)—mm	16.0 (13.5–20.5)	16.0 (13.0–24.0)	0.61
Arm muscle circumference (median)—cm	30.0 (25.5–33.0)	28.0 (21.0–33.0)	0.10
Waist circumference (mean)—cm	101.1 ± 14.2	93.1 ± 11.92	0.05

Between brackets—interquartile rate

Table 3 Study of anthropometric parameters of patients with spondyloarthritis (SpA). Comparison with controls and study of influence of anti-TNF use

Comparison of SpA patients with controls			
Variable	SpA (<i>n</i> = 44)	Control group (<i>n</i> = 62)	<i>p</i>
Body mass index—kg/m ² (median)	27.9 (23.79–31.50)	24.4 (22.58–27.88)	0.003
Tricipital skin fold—mm (median)	18 (14–21.7)	27.0 (21.7–34)	< 0.0001
Arm muscle circumference—cm (mean)	24.2 ± 4.48	22.4 ± 4.27	0.03
Waist circumference—cm (median)	95.5 (90–104.8)	87.5 (82–100)	0.004
Comparison of SpA patients treated with and without anti-TNF			
Variable	SpA with anti-TNF (<i>n</i> = 23)	SpA without anti-TNF (<i>n</i> = 21)	<i>p</i>
Body mass index—kg/m ² (median)	26.2 (22.6–31.7)	31.9 (26.3–30.9)	< 0.0001
Tricipital cutaneous fold—mm (median)	14.0 (11.0–20.0)	18.0 (16.5–24)	0.007
Arm muscle circumference—cm (mean)	24.2 ± 4.42	24.2 ± 4.66 cm	0.95
Waist circumference—cm (mean)	93.22 ± 9.62	101.2 ± 12.63 cm	0.02

Between brackets—interquartile rate

In patients with SpA, our study showed an increase in the prevalence of overweight and obesity in relation to the control population, as well as an increase in abdominal waist diameter. Studies that portray the nutritional profile in SpA are scarce in the literature. Briot et al. [18] following patients with SpA for two years found that anti-TNF α therapy resulted in a considerable increase in body weight, mainly due to a higher proportion of fat. In addition, Di Renzo et al. [19] reported that a group with the psoriatic form of SpA using anti-TNF α showed increased BMI due to increased fat but also to muscle mass. These two studies contradict the results of the present investigation, which show a reduction of BMI and WC in patients controlled by the use of biological therapy, without significant alteration in muscle mass standard. However, it is worthwhile to note that, in this form of disease, it is possible that the kyphotic posture adopted by patients with advanced SpA contributed partially to the increase of the abdominal diameter and this may have influenced the results.

As it can be observed, in the present study, there are disagreements between the nutritional findings of patients using anti-TNF with RA and with SpA. While in the first this drug does not cause any changes, in the second, it promotes a decrease in fat and an increase in muscle mass. What could justify these differences? Firstly, it is interesting to consider that although TNF α is a key cytokine in the inflammatory process of these two diseases, there are important differences among them from a pathophysiological point of view. Second, glucocorticoids are more commonly used in RA and are maintained for a longer time. In SpA, its use is limited to the treatment of extra-articular manifestations, mainly the ocular ones, being done intermittently and in general, for small periods of time. It is possible that the greater use of glucocorticoids in patients with RA attenuates possible beneficial effects of anti-TNF α .

The nutritional status of patients with CD has the peculiarity of being influenced not only by a chronic inflammatory

Table 4 Study of anthropometric parameters of patients with Crohn's disease (CD). Comparison of CD patients with controls and between CD patients using and not using anti-TNF drugs

Comparison of CD patients with controls			
Variable	CD patients (<i>n</i> = 44)	Control group (<i>n</i> = 63)	<i>p</i>
Body mass index—kg/m ² (median)	25.5 (22.8–30.9)	24.1 (22.1–26.4)	0.03
Tricipital skin fold—mm (mean)	20.2 (4.5–67.7)	26.3 (8–55)	0.001
Arm muscle circumference—cm (mean)	26.2 ± 6.32	21.4 ± 4.58	< 0.0001
Waist circumference—cm (mean)	93.6 ± 13.0	87.4 ± 14.9	0.02
Comparison of CD patients treated with and without anti-TNF			
Variable	CD with anti-TNF (<i>n</i> = 20)	CD without anti-TNF (<i>n</i> = 23)	<i>p</i>
Body mass index—kg/m ² (median)	26.8 ± 6.4	27.1 ± 4.34	0.87
Tricipital skin fold—mm (mean)	21.4 ± 13.7	19.2 ± 7.75	0.53
Arm muscle circumference—cm (mean)	25.5 ± 3.9	26.9 ± 8.3	0.48
Waist circumference—cm (mean)	91.9 ± 15.02	95.1 ± 11.1	0.41

Between brackets—interquartile rate

process, but also of the involvement of the intestinal gastrointestinal tract—which has a fundamental role in the nutrient absorption. Despite this, it is observed that, with the advent of biological drugs, overweight and obesity began to have a higher prevalence in these patients as described by Wiese et al. [20]. These last authors observed an increase of weight in patients with CD after 6 months of use of infliximab, not distinguishing if it was due to muscle mass or fat [20].

In the present study, no significant changes in nutritional status of CD patients using anti-TNF treatment in comparison with immunosuppressant drugs were noted. However, it can be observed that the CD group in remission, as a whole, presented a mean weight above controls and with larger WC, repeating the findings of the RA and SpA groups.

Recently, the obesity pandemic has troubled the world in both developed and developing countries, resulting in high morbidity and mortality due to cardiovascular disorders, diabetes mellitus, metabolic syndrome, and cerebral vascular events [21–23]. In this context, the distribution of fat tissue seems to be more important than the amount of the fat itself, as central abdominal obesity is associated with insulin resistance, increased type 2 diabetes mellitus, and other complications [24]. In the present study, even the control group had a higher BMI than desired. Even so, patients with inflammatory disease in remission exceeded the controls not only in BMI, but also in central obesity, demonstrating a great need for health professional interference in this regard. Guidelines highlighting the importance of regular physical activities, dietary care, and body weight control should be part of the routine outpatient care of patients with RA, CD, and SpA.

This study has limitations. It is a cross-sectional study and has a low number of patients, both in biological therapy and using conventional treatments. In addition, it did not take into account the time of use of biological treatment of each patient. Also, more sensitive methods of body mass determination such as bioimpedanciometry and tomography could bring more data for analysis since they determine body composition more reliably. However, despite these limitations, it makes clear the existence of the obesity problem in the patient with chronic disease in remission and emphasizes the need for a vigorous performance of the health professional in this regard.

Concluding, our study detects high prevalence of overweight and obesity in patients with inflammatory diseases at the stage of remission either by the use of biological or immunosuppressive drugs. A concomitant accumulation of abdominal fat with a decrease in PCT in patients with RA, CD, and SpA was also demonstrated. Centripetal obesity in RA and CD may be related to the prolonged use of corticosteroids found in these patients. No significant influence of anti-TNF α was observed on the anthropometric findings of the RA and CD groups compared to the immunosuppressive group. However, in SpA patients using biologicals, the nutritional

parameters (BMI, CA, and PCT) were significantly better, suggesting a positive impact of biological therapy on the nutritional profile of this group of patients.

Compliance with ethical standards

This cross-sectional study is approved by the local Committee of Ethics in Research. All participants signed consent and were over 18 years of age.

Disclosures None.

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