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Body composition and functional capacity in patients with Crohn's disease using Infliximab

Composição corporal e capacidade funcional de pacientes com doença de Crohn em uso de Infliximabe

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Abstract

Rationale: *the use of anti-TNFα therapy, such as Infliximab (IFX), in patients with Chron's disease (CD) can lead to changes in body composition.* ***Objective:*** *to evaluate the body composition and functional capacity of patients with CD.* ***Method:*** *Cross-sectional study with patients with CD in clinical remission using IFX. For anthropometric evaluation, it was measured: weight, height and waist circumference; functional capacity by the hand grip strength test and body composition by bioelectric impedance. After that, the fat-free mass index and body fat index were calculated. Continouns variables were analyzed by Pearson or Spearman coefficient. For the multiple linear regression model, the time of use of IFX was used as a dependent variable and waist circumference, fat-free mass index, phase angle and handgrip strength were used as independent variables.* ***Results:*** *forty-three patients were evaluated, with an average of 43.1± 13.5 years of age. Of the total, 44.2% were overweight and 44.2% had increased waist circumference, 58.1% were classified with high to very high fat-free mass, 30.2% were below the adequacy parameter for fat-free mass index and 11.6% had reduced functional capacity.* ***Conclusion:*** *overweight, as well as increased waist circumference and body fat, is common in CD patients in clinical remission using Infliximab. Most patients had preserved functional capacity, however there wasn't association with time of use of IFX.*
Keywords*: Crohn disease; body composition; muscle strength; infliximab.*

Resumo

Introdução: o uso de terapia anti-TNFα, como o Infliximabe (IFX), em pacientes com doença de Chron (DC) pode levar a alterações na composição corporal. **Objetivo:** avaliar a composição corporal e capacidade funcional de pacientes com DC. **Metodologia:** estudo transversal com pacientes com DC em remissão clínica, em uso de IFX. Foi realizada avaliação antropométrica (peso, estatura e circunferência da cintura); avaliação de capacidade funcional (teste de força de pressão manual); e avaliação de composição corporal (impedância bioelétrica) com cálculo do índice de massa livre de gordura e índice de gordura corporal. Variáveis contínuas foram analisadas pelo coeficiente de correlação de Pearson ou Spearman. Para o modelo de regressão linear múltipla, o tempo de uso do IFX foi utilizado como variável dependente e circunferência da cintura, índice de massa magra, ângulo de fase e força de preensão manual foram utilizados como variáveis independentes. **Resultados:** foram avaliados 43 pacientes, com média de idade de 43,1± 13,5 anos. 44,2% estavam acima do peso e 44,2% possuíam circunferência da cintura aumentada, 58,1% foram classificados com índice de gordura corporal de alto a muito alto, 30,2% estavam abaixo do parâmetro de adequação para o índice de massa livre de gordura e 11,6% apresentaram capacidade funcional reduzida. **Conclusão:** o excesso de peso e o aumento de circunferência da cintura e gordura corporal é frequente em pacientes com DC em remissão clínica e em uso de IFX. A maioria dos pacientes apresentou capacidade funcional preservada, porém não houve associação com o tempo de uso do IFX.
Palavras-chave: doença de Crohn; composição corporal; força muscular; infliximab.

INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) with transmural involvement that can affect from the mouth to the anus[1]. Traditionally it was considered a disease of developed and "Westernized" nations, but recent studies have shown it increased in incidence in rapidly industrializing countries in Asia, Africa and Australasia. In Brazil, there is an increase in the incidence and prevalence of CD over time and it's higher in the developed states of the country as compared with the states with the lowest development index in Brazil[2].

Although IBD envolves with malnutrition and weight loss, currently overweight and obesity are the most

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frequent nutritional disorders in these population, especially in the remission phase of the disease[1,3,4]. One of the possible factors for this occurrence is the introduction of anti-TNF-α therapy, such as infliximab (IFX) [5].

When compared with conventional therapy, IFX treatment promotes sudden and prolonged regulation of inflammation, stimulating mucosal healing. In this way, it promotes the recovery of nutritional status with weight gain and increase in strength and muscle mass[6–10]. However, after six months of treatment, patients have a significant increase in abdominal obesity and body fat[7].

Changes in body composition such as excess weight and reduced muscle mass increase the chances of loss of response to anti-TNF-α therapy in patients with IBD, since they alter the pharmacokinetics of the drug[11,12]. Therefore, the aim of the study was to evaluate the body composition and functional capacity of patients with CD in clinical remission using IFX. This study will serve as a basis to substantiate the nutritional approach, contributing to the effectiveness of drug therapy and better clinical prognosis for patients.

METHODOLOGY

SAMPLE

This is a cross-sectional study with patients with CD in clinical remission using IFX. The study was developed at the IBD outpatient clinic of the hospital de Clínicas of the Federal University of Paraná. The outpatient clinic is a reference center in the state of Paraná in the care of patients with IBD.

This research was approved by the Ethics Committee in research with human beings (No. 63801717.0.0000.0096), developed according to the ethical criteria of Resolution 466/2012 of the National Health Council of the Ministry of Health (Brazil). The recruitment period of patients for the survey was from August 2018 to July 2019.

Patients with CD, using IFX, of both sexes, aged 18 to 65 years, in the phase of clinical remission of the disease were included in the study according to the Harvey-Bradshaw's Index (score ≤ 4) and/or the clinical diagnosis of remission recorded in the medical record by the gastroenterologist. All patients who agreed to participate in this work signed the Informed Consent Form.

Patients with active CD; using diuretics; with recent surgeries in the gastrointestinal tract (≤ 3 months); in IFX induction protocol; with metal prostheses; with pacemaker; with kidney diseases, cancer, liver diseases and other diseases with manifestation of inflammation, pregnant women and those who did not want to participate in the research were excluded from the study.

For the clinical characterization of CD, the following medical records were collected: CD time (years), location and behavior of CD, bowel resection surgery, bowel resection location, Harvey-Bradshaw's Index score and IFX treatment time (years).

The sample calculation was performed in the program G Power Windows 3.1.9.2[13]. The statistical multiple linear regression test was considered: fixed model, R^2 deviation of zero, effect size of 0.35 (wide), error α of 0.05, sample power (1 – β) of 0.8, of which four predictors, totaling 40 patients.

ANTHROPOMETRIC ASSESSMENT

Body mass was measured in the morning on an anthropometric scale with a maximum capacity of 150 Kg and a variation of 100 g (Welmy®). The height was measured using a mobile stadiometer attached to the scale with millimeter accuracy.

Body Mass Index (BMI) was calculated. Cut-off points established by the World Health Organization were considered[14].

Waist circumference was measured using a flexible anthropometric tape with an accuracy of 0.1 cm (Cescorf®). The cut-off points established by the WHO were adopted (women: ≥ 80 cm, men: ≥ 94 cm)[14].

ASSESSMENT OF BODY COMPOSITION

To assess body composition, the Biodynamics 450® bioelectric impedance device with 800μA and 50 KHz was used. Telephone contact was made the day before the consultation for guidance on how to perform the exam.

From resistance (R) and reactance (Xc) data, fat-free mass[15], body fat[16] and phase angle[17] were calculated.

For the calculation of the fat-free mass index and body fat index, the values of fat-free mass and body fat, respectively, were divided by height squared, with the body mass in kilograms and the height in meters. The cut-off points of Kyle et al. [18] (2005) were used to assess fat-free mass index (women: ≤ 15 kg/m², men: ≤ 17.4 kg/m²) and body fat index (women: ≥ 8.2 kg/m², men: ≥ 5.2 kg/m²).

FUNCTIONAL CAPACITY ASSESSMENT

To evaluate the functional capacity, the handgrip strength was measured using the Jamar® analog hydraulic dynamometer.

Three consecutive measurements were taken with the non-dominant hand with a 30-second rest interval between each measurement[19]. The average value between the three attempts was assumed. The reduction of muscle mass was defined by handgrip strength < 5th percentile by age and sex according to the cutoff points of Budziarek, Duarte, Barbosa-Silva [20] (2008).

STATISTICAL ANALYSIS

For statistical analysis, SPSS version 22.0 was used. The Shapiro-Wilk test was considered to evaluate the normality condition of the variables. Variables with normal distribution were described in average and standard deviation and non-normal distribution in median or con-

fidence interval, minimum and maximum. To compare variables between sex, Student t test or Mann-Whitney U test were used.

Categorical variables were analyzed by frequency calculation. To verify the correlation between variables categories, The Chi-square test of independence was used. The correlation between continuous variables was analyzed by Pearson or Spearman coefficient.

For the multiple linear regression model, the time of use of IFX was used as a dependent variable. Waist circumference, fat-free mass index, phase angle and handgrip strength were used as independent variables. Values of p < 0.05 indicated statistical significance.

The elaboration of the article followed the STROBE system (STrengthening the Reporting of OBservational studies in Epidemiology) for cross-sectional study.

RESULTS

Sixty-three patients with CD in clinical remission and using IFX were invited to participate in the study, but 20 of them were excluded because they did not meet the inclusion criteria, totaling 43 patients. Of these, 53.5% (n=23) were female with a mean age of 43.1± 13.5 years, with no significant difference between the sex (p=0.069).

The average time of diagnosis of CD was 14.1 ± 8.0 years and 5.6 (0.3 – 21.7) years when using IFX, and the age at diagnosis was 26.0 (2.0 – 54.0) years. There was no significant difference between the time of CD, the time of use of IFX and the age at diagnosis of CD, when compared by sex (p= 1.000, p= 0.874 and p= 0.150, respectively).

The other clinical characteristics, such as age at diagnosis, according to the Montreal Classification criteria, location and behavior of the disease Harvey-Bradshaw's Index score and frequency of bowel resection surgery, are described in Table 1.

Table 1 – Clinical characteristics of patients with Crohn's disease in remission using infliximab.

Variables	Total (n=43) % (n)
Age at diagnosis (years)	
≤ 16 y	16.3 (7)
17 – 40 y	65.1 (28)
≥ 40 y	18.6 (8)
Disease Location	
Ileal	16.3 (7)
Colonic	32.6 (14)
Ileocolonic	46.5 (20)
Ileocolonic + upper gastrointestinal tract	4.7 (2)
Crohn's Disease Behavior	
Non-stricturing, Non-penetrating	11.6 (5)
Stricturing	27.9 (12)
Stricturing + "p"	2.3 (1)
Penetrating	2.3 (1)
Penetrating + "p"	20.9 (9)
Stricturing and Penetrating	14.0 (6)
Stricturing and Penetrating + "p"	20.9 (9)
Bowel resection	41.9 (18)
Large intestine	61.1 (11)
Small + Large intestine	38.9 (7)
Harvey-Bradshaw's Index *	0.69 ± 1,1

Notes: 4 patients were not included in the calculation of the Harvey-Bradshaw's Index. There was no statistical difference between the Harvey-Bradshaw's Index when compared by sex (*p* – Harvey-Bradshaw's Index: 0.778). Variables with normal distribution are described in average and standard deviation. Caption: "p": perineal.

Regarding the other characteristics related to nutritional status, it was observed that 44.2% (n=19) of the patients were overweight and obesity (BMI ≥ 25 kg/m^2), 44,2% (19) had increased waist circumference and 58.1% (n=25) were classified with high to very high body fat index.

It was identified that 30.2% (n=13) presented low value for fat-free mass index and 11.6% (n=5) – all were male – presented reduced functional capacity (Table 2).

Table 2 – *Describes the data of anthropometry, body composition and functional capacity of the study participants*

Variables	Total (n=43)	Female (n=23)	Male (n=20)	*p*
Body mass (kg)	65.4 ± 11.9	60.9 ± 10.6	70.7 ± 11.3	0.00*
Height (m)	1.63 ± 0.1	1.57 ± 0.76	1.72 ± 0.7	0.00*
BMI (kg/m^2)	24.4 ± 3.7	24.8 ± 3.6	24.0 ± 3.9	0.45
BMI (≥ 25.0 kg/m^2) % (n)	44.2 (19)	43.5 (10)	45.0 (9)	0.90
Waist circumference (cm)	84.1 ± 10.7	82.5 ± 10.4	86.0 ± 11.0	0.29
Increased Waist circumference % (n) [1]	44.2 (19)	62.5 (15)	20.0 (4)	0.00*
Body Composition				
Fat-free mass (kg)	46.2 ± 9.0	39.6 ± 5.7	53.7 ± 5.5	0.00*
Fat-free mass (%)	70.8 ± 8.1	65.4 ± 5.9	76.7 ± 6.0	0.00*
Fat-free mass index (kg/m^2)	17.1 ± 2.0	16.1 ± 1.7	18.2 ± 1.9	0.00*
Low Fat-free mass index % (n)[2]	30.2 (13)	26.1 (6)	35.0 (7)	0.19

Body fat (kg)	19.3 ± 6.8	21.2 ± 6.5	17.0 ± 6.5	0.04*
Body fat (%)	29.2 ± 8.1	34.3 ± 5.9	23.2 ± 6.0	0.00*
Body fat index (kg/m²)	7.3 ± 2.8	8.7 ± 2.5	5.8 ± 2.2	0.00*
High to very high body fat index % (n)[3]	58.1 (25)	52.2 (12)	65.0 (13)	0.39
Phase angle (°)	6.6 ± 1.1	6.4 ± 1.2	6.8 ± 0.9	0.17
Handgrip strength (kgf)				
Dominant hand	24.7 (14.0 – 52.7)	20.3 (14.0 – 31.3)	39.2 (22.3 – 52.7)	0.00*
Non-dominant hand	25.0 (13.0 – 47.0)	19.6 (13.0 – 35.0)	34.8 (23,0 – 47.0)	0.00*
Reduced handgrip strength % (n)[4]	11.6 (5)	0.0 (0)	25.0 (5)	0.01*

*Notes: Variables with normal distribution are described in average and standard deviation and variables with non-normal distribution are described in median and minimum and maximum median. For comparison between groups, the Student t-Test or Mann-Whitney U-Test were used. To verify the association between variables categories, The Chi-square test of independence was used. *Indicates significant difference (p < 0.05). Caption: BMI: body mass index, cm: centimeters, kg: kilos, m: meters, kgf: kilogram-force. 1) increased waist circumference: women: ≥ 80 cm and men: ≥ 94 cm; 2) low fat-free mass index: women: ≤ 15 kg/m², men: ≤ 17.4 kg/m²; 3) high to very high body fat index: Women: ≥ 8.2 kg/m² and men: ≥ 5.2 kg/m² and 4) reduced handgrip strength: women – age between 18 to 30 years: < 13 kgf), 31-59 years: < 10 kgf, ≥ 60 years: < 10 kgf) and men – age between 10 and 30 years: < 30 kgf, 31-59 years: < 26 kgf and ≥ 60 years: < 18 kgf).*

It was found that the longer the time of use of IFX, the higher the BMI (p=0.043; r=0.310) and waist circumference (p=0.018; r=0.359). However, the multiple linear regression model was not significant (p=0.150), considering the time of use of IFX as a dependent variable and the independent variables: waist circumference, fat-free mass index, phase angle and handgrip strength.

DISCUSSION

The results of this study indicate that overweight and obesity and abdominal obesity are common, as well as increased body fat in patients with CD in clinical remission and using IFX. It also highlights that about 30% of these patients had a reduction in fat-free mass.

The high prevalence of overweight and obesity found in this study is consistent with the current scenario in which obesity is the most frequent nutritional disorder in patients with IBD [3,4,21,22]. It is known that between 15% and 40% of IBD population are obese [21].

Ramos et al.[23] (2019) also found a high prevalence of overweight and abdominal obesity in patients with CD in clinical remission and in therapy with anti-TNF-α, the frequency of overweight and obesity (BMI ≥ 25 kg/m²) was 55.7% in patients with CD versus 41.2% in the control group of healthy individuals (p < 0.0001). In the study of Magro et al.[24] (2018), the prevalence of overweight and obesity in patients with CD was 42%, where 67% were using anti TNF alpha therapy. This is similar to the findings in our study.

Probably, patients with CD in remission and using IFX are one of the first affected by the nutritional transition, since symptom control and reduction of catabolism associated with inflammation are maintained for a longer period of time when compared to conventional drug therapy[8]. In addition to the drug's previously mentioned physiologic action, a sedentary lifestyle and poor eating habits can contribute to weight gain. The adoption of western nutritional habits characterized by an overall higher calorie consumption that is primarily made up of sugar, refined carbs, animal proteins, and ultraprocessed foods has been associated with higher risk of obesity[25].

Associated with increased body fat, about 30% of patients presented low fat-free mass index. Similar results were observed by Back et al. [26] (2017) in which the average fat-free mass index in patients with CD in clinical remission (n=30) was 18.5 ± 2.8 kg/m². The increase in obesity in IBD patients coincides with the increase in rates of sarcopenia, which is defined as low lean mass (myopenia) and loss of strength[27,28]. A systematic review reported that 42.0% of IBD patients were sarcopenia and this condition affects the prognosis, such as rehospitalization, death and several infections [29,30]. Overweight and sarcopenia may influence the response to biological therapy by altering the pharmacokinetics of the drug [11,25].

In a meta-analysis study with 4,589 IBD patients on anti-TNF-α therapy, it was found that IBD patients with obesity had a 19.5% greater chance of loss of response to anti-TNF-α therapy [11]. As well as obesity, myopenia in patients with CD, when inserted in the multivariate analysis with albumin, was associated with loss of primary response to anti-TNF-α therapy within 6 months after the first administration, not including patients who stopped treatment due to intolerance to the therapy [12].

Although the body composition was altered, only 11.6% of the patients had reduced functional capacity. The use of IFX may be associated with anabolism and consequent increase in strength and muscle mass [7,10]. Cabalzar et al. [31] (2019) found that patients with moderate to severe CD in IFX-induced clinical remission for at least 6 months had normal functional capacity according to the handgrip strength test performed with the dominant hand.

Although fat-free mass depletion is frequent in patients with IBD in remission, it is possible that in the subgroup of patients on biological therapy with IFX this is not a marked change due to the anabolic effect of IFX [7,10]. The increase in fat-free mass is significantly higher in patients on IFX therapy when compared to patients in clinical remission and on conventional therapy [8].

The fat-free mass has a positive correlation with the phase angle in patients with CD, this being greater in patients in remission of the disease[32]. The average phase angle found was similar to the findings of Cioffi et al. [32] (2019) in the group of patients with CD in biological therapy.

The phase angle is an indicator of good nutritional status[33]. In our study, the mean phase angle in both sexes indicate absence of malnutrition according to the cutoff points suggested to patients with CD reported by Peng et al.[33] (2022). Emerenziani et al. [8] (2017) found greater phase angle in patients with CD in clinical remission on IFX treatment compared to patients on conventional therapy.

In this study, it was found that the longer the time of use of IFX, the higher the BMI and waist circumference. Despite the beneficial effect on the recovery of nutritional status, which is already observed from the beginning of the IFX induction protocol until the maintenance[8,9]. Santos et al.[7] (2017) found significant increase in BMI (22.9 ± 3.2 versus 25 ± 3.8 kg/m^2; p = 0.005), waist circumference (88.1 ± 6.7 versus 93.9 ± 7.7 cm; p = 0.002) and body fat index (5.5 ± 2.3 versus 6.8 ± 2.3 kg/m^2; p = 0.000) after 6 months of treatment with anti-TNF-α therapy.

This study has limitations such as the reduced number of participants. However, the use of anthropometry associated with bioelectric impedance can help in the understanding of body changes in patients with CD using IFX. In addition, the use of bioletric impedance has as advantages in clinical practice: the low cost and practicality.

Since the imbalance in body composition can influence the loss of response of biological therapy and the development of chronic non-communicable diseases, it becomes essential to substantiate the nutritional approach.

CONCLUSION

The high frequency of overweight, as well as the increase in body fat, signaled by the increased waist circumference are related to the time of use of IFX in patients with CD in clinical remission. Most patients had preserved functional capacity, however there wasn't association with time of use of IFX.

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