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Original article

Lower skeletal muscle attenuation and high visceral fat index are associated with complicated disease in patients with Crohn's disease: An exploratory study

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SUMMARY

Background and aims: The prognostic value of body composition analysis in patients with Crohn's disease (CD) is poorly explored. The aims of the present study were to assess fat and skeletal muscle compartments including muscle radiation attenuation (MA) in patients with CD, and to analyze its predictive value to identify complicated phenotypes.

Methods: Seventy one patients with CD who have had an abdominal CT within one month of clinical, laboratory, and endoscopic evaluation were included. Skeletal muscle area (SMA) and index (SMI), visceral fat area (VFA) and index (VFI), subcutaneous fat area (SFA), and mean MA were measured using appropriate software. Sarcopenia, as defined by Martin's criteria was assessed. Montreal classification was used to characterize disease phenotype.

Results: Mean MA was lower in patients >40 years ($p = 0.001$), L2 ($p = 0.09$) and stricturing/penetrating disease ($p = 0.03$) whereas SMA and SMI were significantly lower in patients with positive C-reactive protein and previous hospital admissions ($p < 0.01$). On multivariate analysis, higher MA was protective against the complicated disease phenotype (stricturing/penetrating disease and/or previous surgeries) (OR 0.81; $p = 0.002$) whereas a high visceral fat index increased such risk (OR 26.1; $p = 0.02$). A ROC curve showed a 82.4% sensibility, 90.3% specificity, 17.6% positive predictive value, 9.7% negative predictive value and an area under the curve (AUC) of 0.91 for body composition analysis to predict complicated disease.

Conclusions: A lower muscle attenuation and a high visceral fat index seem to be associated with more severe phenotypes in patients with CD.

1. Introduction

In recent years, the relationships between body composition and clinical outcomes have been extensively studied in the field of oncology, facilitated by the advent of appropriate software applied to diagnostic imaging technologies such as computed tomography (CT). Body composition parameters such as sarcopenia, visceral obesity, and muscle infiltration by fat are now recognized as important prognostic factors predicting toxicity and response to chemotherapy, postoperative complications and even survival, more accurately than other variables classically associated to a better prognosis such as TNM stage [1–5].

Changes in body composition evaluated by various methods such as computed tomography, magnetic resonance or abdominal ultrasound, have also been described in Crohn's disease (CD), but their clinical significance and predictive value remain unclear [6,7]. Changes in mesenteric fat, also known as fat wrapping, have been recognized in patients with CD since its initial description [8].

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Studies performed during the last decade show that increased body mass index in CD patients is associated with poorer prognosis, early need for surgery, higher risk of active disease and earlier loss of response to therapy [9–11]. Further supporting the active role of mesenteric fat in promoting intestinal inflammation, recent studies showed that visceral fat in patients with CD undergoing intestinal resection was associated with higher risk of postoperative complications and postoperative recurrence [6,12]. However, whether visceral fat accumulation is a consequence of long standing disease or a primary event involved in the pathogenesis of the disease is still unclear [13,14]. Sarcopenia (severe muscle depletion) has been shown to be highly prevalent in CD, possibly as a result of poor nutrition, uncontrolled inflammation, and physical inactivity among others [15], and to be associated with major postoperative complications. Treatment with anti-TNF was shown to reverse sarcopenia, further supporting the concept that it may represent a biomarker of chronic inflammation and wasting [16]. Finally, skeletal muscle radiation attenuation (MA) is a radiologic metric inversely related to muscle fat content [1]. A reduction in MA, mirroring excess fat deposition in the muscle tissue, has been described in several chronic inflammatory conditions such as obesity, type 2 diabetes, and in cancer patients [1], in whom it is associated with a poorer prognosis [2]. The value of these body composition variations, as markers of chronic inflammation and in predicting more severe phenotypes in patients with CD has not been previously tested. The aims of the present study were to perform a comprehensive description of the skeletal muscle and fat compartments in patients with CD, to analyze the recently described variable MA, and to explore possible associations of these body composition measurements with complicated phenotypes with the aim of assessing its potential use as early predictors of severe disease.

2. Materials and methods

2.1. Study population

The study protocol was approved by the Scientific and Ethics Committee of Hospital Beatriz Ângelo in Loures, Portugal. We retrospectively reviewed all the clinical records of CD patients followed in our clinic between 2012 and 2015. Patients were included if they had a computed tomography enterography (CTE) or computed tomography ordered as part of clinical workup within one month of full clinical, laboratorial and, whenever possible, endoscopic evaluation. Phenotypic characteristics retrospectively collected from charts included demographic data, age of disease onset, disease extension, and behavior according to Montreal classification [17], and previous therapies including surgery. Patients with a history of a stricturing (B2) or penetrating (B3) complication and/or previous resection surgery at any time point during their clinical course were considered as having a complicated phenotype. Laboratory values were abstracted from electronic charts. Anemia defined as a hemoglobin value lower than 12 g/dl for women or 13 g/dl in men. C-Reactive protein (CRP) was considered positive when higher than 0.5 mg/dl.

2.2. Cross-sectional imaging evaluation

CT scans were obtained and evaluated for body composition data by two investigators who were blinded to clinical and endoscopic data to ensure objective interpretation of image findings. Skeletal muscle and fat tissue cross-sectional areas were measured on CT images, at the level of the third lumbar vertebrae (L3) with the patient lying supine as shown in Fig. 1. Skeletal muscle area (SMA), visceral fat area (VFA) and subcutaneous fat area (SFA) were measured in square centimeters on the basis of the pixel count using appropriate software [2]. Briefly, muscle is annotated and is quantified within a Hounsfield unit (HU) ranging from −29 to 150; visceral fat ranges from −150 to −50 HU, and subcutaneous fat from −190 to −30 HU. Muscle radiation attenuation was calculated for muscle area from −190 to −30 HU. Skeletal muscle area (SMA) was normalized for stature to calculate the skeletal muscle index (SMI) − cm^2/m^2. Visceral Fat Index (VFI) was defined as the ratio of areas of visceral to subcutaneous fat. Sarcopenia was defined as SMI lower than 41 cm^2/m^2 in women, lower than 43 cm^2/m^2 in men with body mass index (BMI) < 25 kg/m^2 and <53 in men with BMI ≥ 25 kg/m^2 as described by Martin et al. [2] based on the International Consensus of Sarcopenia [18]. Visceral obesity was defined as visceral fat area > 130 cm^2 [19].

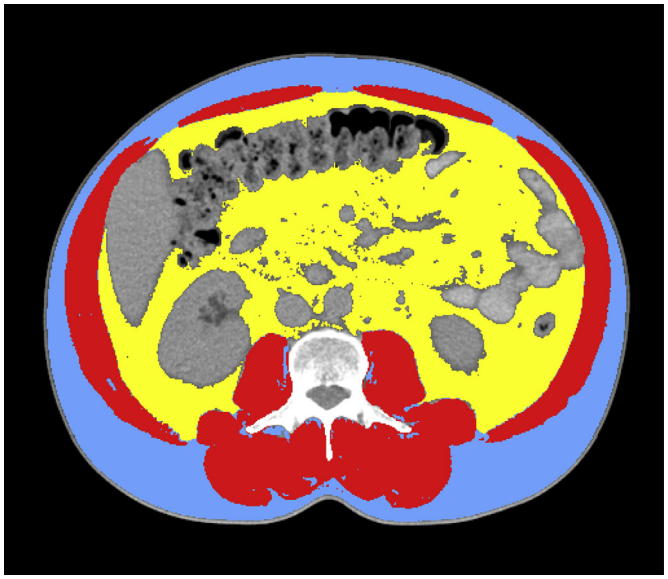

Fig. 1. Axial computed tomography (CT) images at the level of the third lumbar vertebrae were analyzed for muscle and fat tissue cross sectional areas and analyzed using an appropriate software. Muscle mass is shown in red and was quantified within a Hounsfield unit (HU) range of −29 to 150, visceral fat shown in yellow, range from −150 to −50 and subcutaneous fat shown in blue range from −190 to 30. Muscle radiation attenuation was calculated for muscle area.

2.3. Statistical analysis

Continuous variables were described as mean, median and range, while categorical variables were expressed as frequency and percentage. Differences in mean continuous variables and dichotomous variables were analyzed by *t*-test or Mann Whitney *U* test as appropriate, according to variable's adjustment to a normal distribution. Difference in mean continuous variables and categorical variables with more than two levels was conducted with One-way analysis of variance (ANOVA) or Kruskal–Wallis test, as appropriate. Chi-squared test and Fisher's Exact Test were used to explore associations between categorical variables. A p-value < 0.05 was considered statistically significant. Univariate logistic regression was first performed using complicated behavior (B1 vs B2 or B3 and/or previous resection surgery) as the dependent variable and clinically relevant factors as independent variables namely gender, age, disease duration and location, weight and BMI, skeletal muscle area, subcutaneous and visceral fat area, visceral obesity, mesenteric fat index, MA and sarcopenia, anemia and CRP positivity.

On multivariate analysis both manual and automatic variable selection methods were preformed. Hosmer and Lemeshow (HL) method was used for manual variable selection, and, as part of this method, a p-value cut-off of 0.25 on univariate analysis was used.

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