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ORIGINAL ARTICLE

Relationship between skeletal muscle function, body composition, and weight loss in patients with advanced pancreatic and gastrointestinal cancers

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Abstract

Background Muscle function and its correlation with body composition and weight loss have not been studied deeply in pancreas and gastrointestinal cancers. This research aims to determine the skeletal muscle function and its relationship with body compartments, significant weight loss, and performance status (ECOG) 0-2 in a population with advanced digestive cancers.

Methods A cross-sectional study was designed to determine the relationship between muscular function, weight loss, and body composition. Patients with advanced digestive adenocarcinomas were evaluated. Muscle strength was examined by hand grip technique and body composition by bioimpedance analysis. Values of hemoglobin and albumin were measured in plasma.

Results A sample of 81 patients was included. They had adenocarcinoma of stomach ($n = 9$), pancreas ($n = 28$), or colorectum ($n = 44$). With regard to skeletal muscle function, sub-maximal strength increased when percentage of weight loss decreased ($p = 0.002$) or when any of the following variables increased: skeletal muscle ($p < 0.001$), waist-hip ratio ($p < 0.001$), body surface area ($p < 0.001$), and body mass index ($p = 0.001$). According to multivariate analysis of these variables, only percentage of weight loss and skeletal muscle remained statistically significant. Endurance had no correlation with any of the variables. Higher weight loss was found in tumors of the upper tract (stomach and pancreas) in comparison with those of the lower tract (colorectal) ($p = 0.005$).

Conclusions In advanced digestive cancer, sub-maximal strength correlated inversely with weight loss and directly with skeletal muscle such as in lung and head and neck cancers. On the other hand, endurance had no correlation with any of the variables considered.

Keywords Digestive cancers · Muscle strength · Body composition · Weight loss

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Introduction

It is expected that in the year 2020, pancreas and colorectal adenocarcinoma should be the second most common cause in cancer mortality [1]. Despite specific treatments over the last 20 years (concurrent radio-chemotherapy, novel agents, and biologic modifiers), metastatic digestive cancer continues being incurable and with a high mortality rate. Pancreatic cancer, particularly, has an overall survival rate at 5 years of one digit considering all stages [2–4].

Performance status (PS) (ECOG) 0-2 is necessary to indicate systemic treatment, especially, chemotherapy (CHT) [5, 6]. Nevertheless, PS is considered a poor predictor for response and toxicity. In patients with advanced gastrointestinal cancers, impairment of skeletal muscle function and body fat

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had correlation with fatigue and poor PS; consequently, they had bad tolerance to systemic treatments [7, 8]. Weight loss ≥ 5% in the last 12 months and cancer-related fatigue have also been considered factors of worse prognosis [9, 10]. However, in patients without fatigue and advanced digestive cancers, the relationship between parameters of skeletal muscle function, body composition, and PS remains unknown.

Our group designed a cross-sectional study to evaluate the relationship between skeletal muscle function and several parameters of body composition.

Material and methods

Study design

This protocol was approved by the Ethics Board of the Bonorino Udaondo Gastroenterology Hospital and met the recommendations stated in the Helsinki Declaration. A cross-sectional study was designed to assess characteristics of skeletal muscle function and body composition in a population suffering from advanced digestive tumors presenting significant weight loss, no fatigue, and PS 0-2.

All these patients were receiving CHT including fluoropyrimidines and were between the 2nd and the 4th cycles of a first line.

Outpatients were examined by clinical oncologists who referred them to a physician of the Palliative Care Section. Patients who met the inclusion criteria were requested to participate in the research study.

The primary objective was to determine the relationship of skeletal muscle function with weight loss and body composition. The secondary objective was to compare the variables included in this study between the upper and lower tract tumors. The inclusion criteria were the following: (1) histology of gastric, pancreatic, or colorectal adenocarcinoma; (2) a population aged 18 or over; (3) PS (ECOG) 0-2; (4) weight loss equal or over 5% during the last 6 months; (5) FNS below 4; (6) absence of continuous therapy with corticosteroids; (7) absence of uncontrolled systemic disease or infection; (8) no defibrillator or cardiac pacemaker; (9) hemoglobin (Hb) ≥ 10.4 g/dl, albumin ≥ 3.4 g/dl; normal parameters of renal and liver function, white blood cell ≥ 3000/mm^3, neutrophils ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, normal ranges of glucose, sodium, potassium, magnesium, calcium, and phosphorus. No patients presented dehydration, edema, or joint disease. All patients signed informed consent and their symptoms were alleviated before being included in the study.

Evaluation of the parameters

Percentage (%) of weight loss and measurement of height Weight loss % was calculated by subtracting basal weight from history stable weight (HSW), and the results were divided by HSW and then multiplied by 100 [11]. A Harpender Statiometer was used in height measurement.

Laboratory Hb, albumin, glucose, ALT, AST, alkaline phosphatase, total and direct bilirubin, total cholesterol, triglycerides, creatinine, BUN, plasmatic electrolytes, calcium, phosphorus, and magnesium were measured in plasma.

Body composition Bioimpedance analysis (BIA) with multifrequency (Inbody 120) was used. Briefly, a low electrical current was passed through handlebars with two electrodes on each hand and one on each foot. The patient stood on a step, bare-feeted, and held the handlebars so that the four fingers wrapped the surface of the handlebar containing the electrode, and placed the thumb on the other electrode.

The variables of body composition were registered in a Lookin' Body 120 program. The measurements of body composition were the following: skeletal muscle (kg); total body fat (kg and %), waist-hip ratio; body weight, body mass index (BMI).

Body surface area (BSA) was calculated by means of a formula: $[(\text{height (cm)} \times \text{weight (kg)})/3600]^{1/2}$.

Parameters of skeletal muscle function Electronic hand dynamometer (MODEL NO: EH101) was used for examination of these parameters. Sub-maximal strength and endurance (resistance to fatigue) were examined in the non-dominant hand by hand grip technique. Handgrip strength (HGS) is the register of sub-maximal voluntary contraction (sub-maximal strength). The latter was measured having the patient sitting on a chair, shoulders in slight adduction and elbow flexed at 90°. Three sub-maximal contractions were measured, at intervals of 30 s, being the maximal value the one considered. Endurance was determined by the time, measured in seconds; each patient reduced his/her maximal pressure to half.

FNS The intensity of fatigue in the last 24 h was measured by FNS 0–10. The cutoff under 4 was considered no fatigue. Fatigue word descriptors were lack of energy and weakness [12].

Statistics

A first exploratory analysis was made: the principal variables were assessed and their distribution was determined here. Then, a descriptive analysis of the results was elaborated. Mean and standard deviation were showed for variables with normal distribution; median and 1st and 3rd quartiles were presented when they did not have normal distribution.

Correlations were analyzed graphically and by the Pearson correlation coefficient with its significance test (t test). To accomplish the latter, correlation coefficient (r) and p value were shown. Comparisons of continuous variables between

categories were made by parametric (*t* test) or nonparametric test (median test).

To analyze the relationship between two or more continuous variables, a linear regression model was performed. First, a simple regression model was used to select significant variables. Later, a multiple linear regression model was used to evaluate the relationship between each of those variables. Interactions between variables were studied.

Statistical significance was defined as a two-sided p value < 0.05. Statistical analysis was performed using IBM SPSS Statistics (version 21.0).

Results

Study population and general characteristics

In a period of time of 14 months, 81 patients with upper and lower digestive adenocarcinomas were included. Sixty-seven had metastatic disease while just 5 had locally advanced disease. Nine patients had adenocarcinomas of stomach, 28 of pancreas (the upper tract), and 44 patients of the lower tract (colorectal). All the patients received CHT-based fluoropyrimidines. None of them had surgical possibilities due to metastases (e.g., liver metastases of colorectal cancer). Seventy patients continued CHT after the first re-staging of disease, while 11 did not receive CHT due to disease progression. Table 1 shows the characteristics of the study population.

Table 1 Sociodemographic characteristics of the study patients

Variables	Values
Male, *n* (%)	52 (64.2)
Mean age (sd), yr	57.7 (11.3)
Site, *n* (%)	
Upper GI tract	37 (45.7)
Gastric cancer	9 (11.1)
Pancreatic cancer	28 (34.6)
Colorectal	44 (54.3)
Stage, *n* (%)	
Locally advanced disease	5 (6.2)
Metastatic disease	76 (93.8)
P. status, *n* (%)	
ECOG 0	7 (8.6)
ECOG 1	47 (58)
ECOG 2	27 (33.3)
Median of percentage of weight loss (1Q; 3Q)	9 (7; 15)
Mean BMI (sd), kg/m^2	26.5 (4.9)
Mean of percentage of body fat (sd)	29.2 (9.8)
Mean of skeletal muscle (sd), kg	28.4 (6.2)
Mean of sub-maximal strength (sd), kg	28.6 (9.9)
Median endurance (1Q; 3Q), seconds	30 (20; 40)
Mean hemoglobin (sd), g/dL	12.8 (1.4)
Mean albumin (sd), g/dL	3.9 (0.2)

N number, *sd* standard deviation, *yr* year, *GI* gastrointestinal, *1Q* 1st quartile, *3Q* 3rd quartile

Relationship between parameters of skeletal muscle function and body composition

We evaluated two parameters of skeletal muscle function: sub-maximal strength and endurance. No correlation was found between these two variables ($r = 0.216$; $p = 0.052$). We also analyzed each of these variables with body composition parameters.

Sub-maximal strength was higher for male (mean 33.2 kg) than female (mean 20.3 kg) ($p < 0.001$) (Fig. 1a). It was correlated with skeletal muscle mass, for male ($r = 0.570$; $p < 0.001$) and female ($r = 0.519$, $p = 0.004$) (Fig. 1c). For each sex, sub-maximal strength had a lower or no correlation with the other variables (BMI, body fat, waist-hip ratio, BSA, % of weight loss and albumin) (Fig. 1b). When we evaluated sub-maximal strength by a linear regression model adjusted by sex, we found that skeletal muscle was significant ($p < 0.001$). We also found statistical significance for other variables: BMI ($p = 0.001$), waist-hip ratio ($p < 0.001$), and BSA ($p < 0.001$). On the other hand, percentage of weight loss was also statistically significant but with a negative coefficient ($p = 0.002$). Taking into consideration that sex and skeletal muscle were highly correlated with sub-maximal strength and that they were also significant in the simple linear regression model, we analyzed them in a multiple linear regression model with the other variables (BMI, waist-hip ratio, BSA, and % of weight loss). So, we evaluated each of these, maintaining sex and skeletal muscle variables in the model. Thus, we were able to study the additional information provided by these variables plus sex and skeletal muscle to clarify possible changes in sub-maximal strength. BMI, waist-hip ratio, and BSA were not statistically significant. Only percentage of weight loss still maintained its significance.

Endurance showed a statistically significant difference between sex (mean: male 34.1 s, female 28.0 s, $p = 0.037$) (Fig. 1a). No correlation was found considering endurance and other variables (Fig. 1d). In agreement with these results, we found no significant variable when we analyzed them in a regression model.

Weight loss

Patients with tumors of the upper tract had a higher percentage of weight loss (mean 14.4%) than those with lower tract ones (mean 9.7%) ($p = 0.005$).

Due to the absence of normal distribution, we framed a new categorical variable splitting the population with a cutoff ≥ 10% weight loss. Skeletal muscle, body fat, and BMI were

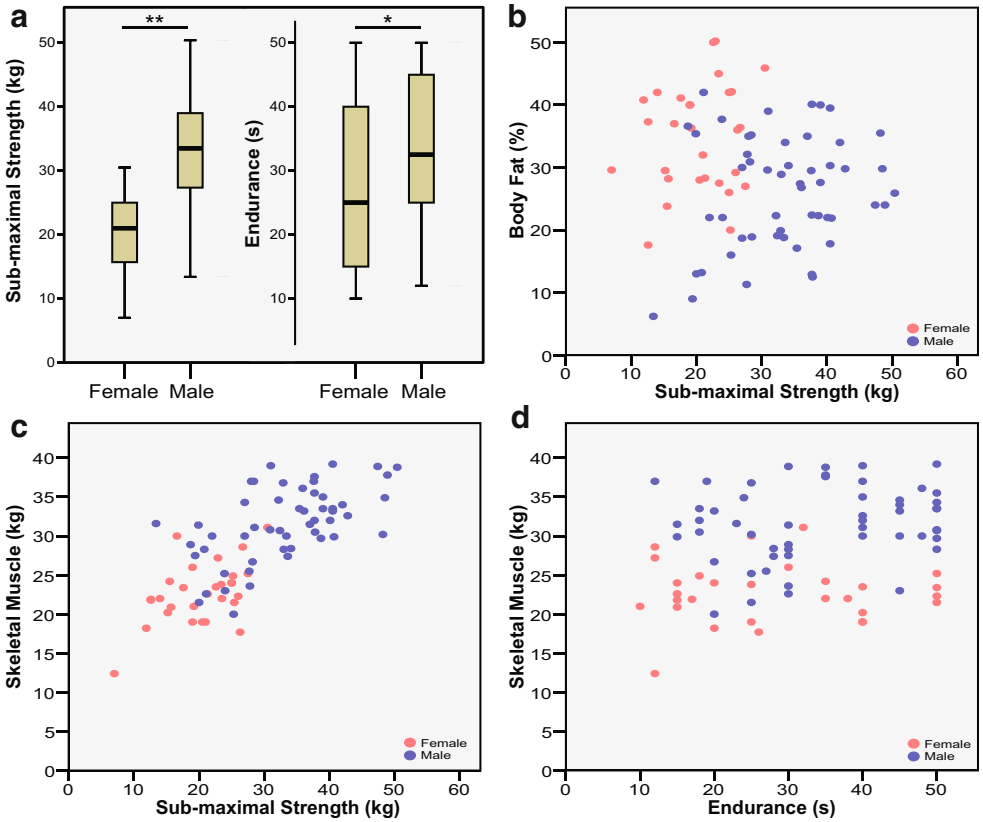

Fig. 1 **a** Submaximal strength and endurance were compared between sex. In both, male had higher scores than female but for submaximal strength, the difference was wider ($p < 0.001$) than for endurance ($p = 0.037$). **b** The scatterplot of body fat and submaximal strength shows a round cloud of dots. It is possible to note the lack of correlation between these variables. Nevertheless, lower values of submaximal strength for females than males were seen. **c** This scatterplot of skeletal muscle and submaximal strength shows a cloud with elliptic shape which means an underlying correlation between these variables. In addition, females had less skeletal muscle and scores of submaximal strength. **d** In the last plot, a square like shape of dots could reveal the absence of correlation between skeletal muscle and endurance. Again, female skeletal muscle values are under males

analyzed between these two categories of weight loss. No statistically significant difference was found.

Relationship between the upper tract and lower tract tumor

There was no difference either with the parameters of body composition or with endurance regarding tumor sites. Patients with upper site tumors had less sub-maximal strength (mean 25.3 kg) than those with lower site ones (mean 31.3 kg) ($p = 0.006$). To evaluate the relationship between the tumor site and the other variables in relation to sub-maximal strength, we analyzed them by a multiple linear regression model. Tumor site was significant ($p = 0.04$) when sex ($p = 0.044$) and skeletal muscle ($p < 0.001$) were included, but tumor site lost significance when we added the weight loss variable.

As previously stated, the upper site tumors had greater percentage of weight loss regarding colorectal tumors.

Discussion

We found that patients achieved higher values of sub-maximal strength when they had more skeletal muscle mass or less percentage of weight loss. Endurance, the other parameter of skeletal muscle function, did not correlate with sub-maximal strength, skeletal muscle, or any other variable. Patients with upper tract tumors had higher percentage of weight loss, as well as lower values of sub-maximal strength.

In our study, the patients had not referred fatigue. Although it was measured by FNS, a simple and validated method for the evaluation of fatigue [13], it is known that half of the patients are reluctant to refer this symptom to the physician for fear of being shifted to a less active treatment [14]. Since endurance is the resistance to fatigue, this could explain, in this population, the absence of correlation between endurance and skeletal muscle as well as with other body composition variables. In a previous study among patients with fatigue and squamous cell carcinoma of head and neck, we found correlation between endurance and significant weight loss [15]. Maybe, it could be considered that a decrease in endurance precedes fatigue. It is known that in advanced illness, the muscle de-conditioning is determinant to the self-perception of fatigue as well as to the impairment of parameters of skeletal muscle function [16, 17]. Additionally, in cancer, sub-maximal strength is strongly associated with skeletal muscle. Muscle strength decreases when ubiquitin proteasome system (UPS) is amplified, because it breaks sarcomere proteins (e.g., myosin heavy chain) producing the loss of muscle cells [18–20]. In elderly people, without cancer, the loss of muscle mass is weakly associated with sub-maximal voluntary contraction and is called by some authors “dynapenia.” Possibly,

this concept should be limited to elderly people and not be applied in cancer to refer to muscle strength impairment [21]. Sarcopenia, in elderly people without cancer, is not the resultant of severe and complex inflammatory state. The latter has been demonstrated in animal models of cancer and partially in clinical studies in humans. According to this, some authors have considered that the UPS is not the main culprit for the loss of muscle in sarcopenia which is the case in advanced cancer [22]. Sarcopenia has been reported in patients with colorectal cancer stages I–II as a risk factor for post-operatory complications in patients over the age of 65 but not in patients under 65; the authors concluded that this population had sarcopenia prior to cancer [23].

Previously, our group found a relationship between endurance and body fat in a sub-population of patients with NSCLC: when the first one decreases the latter also does [17]. In the present study, the preservation of body fat in spite of significant weight loss would be due to a lack of inflammatory state [24].

Weight loss and decrease of muscle strength have been referred as characteristics of digestive upper tract tumors and less frequent in lower tumors [25–27]; we obtained similar results. In fact, we observed that weight loss and tumor site were significant in the univariate analysis but not in the multivariate one. Thus, it could be inferred that both variables provide equivalent information about sub-maximal strength. Whether it is a matter of tumor site or percentage of weight loss remains unclear. It is important to highlight that even when about 50% of patients had more than 10% of weight loss, none of these relationships were found for endurance. The population of this study underwent CHT based on fluoropyrimidines either with capecitabine as monotherapy or with polychemotheray combining fluoruracil with irinotecan and/or oxaliplatin. Others received a combination therapy with gemcitabine and nab-paclitaxel. All the patients were between 2nd and 4th courses. It has already been mentioned that all the symptoms were controlled before being included in the study; therefore, no patients had nausea and/or vomiting at the moment of evaluation. No patients had presented severe nausea or vomiting in the first course that could imply dehydration with impairment of renal function. Besides, the drugs that were administered had either low emetic potential (fluororopyrimidines, irinotecan gemcitabine, nab-paclitaxel) or moderate emetic potential (oxaliplatin) [28, 29].

CHT induced body composition changes cannot be excluded. Nevertheless, in the colon 26 adenocarcinoma murine model, fluoropyrimidines would seem to slow the breakdown of muscle proteins by the UPS [30, 31]. These findings could be considered to understand the preservation of endurance despite significant weight loss in patients with PS 0-2.

A limitation of this study is the absence of measurements of skeletal muscle by computed tomography at level of 3rd lumbar vertebra. As we did not measure inflammation mediators, such as C-reactive protein, interleukina-6 (IL-6), IL-1 beta, or tumor necrosis factor alfa 55sv, we could not establish the relationship between those and other parameters.

In summary, sub-maximal strength has a positive correlation with skeletal muscle and most variables of body composition: a negative correlation with percentage of weight loss. On the other hand, endurance had no statistically significant correlation with sub-maximal strength and weight loss in patients with advanced digestive adenocarcinomas. Finally, stomach and pancreas which are classic examples of wasting tumors showed difference in weight loss but not in body fat and endurance regarding colorectal carcinomas in a sub-population without fatigue and PS 0-2.

Due to the fact that this study is a cross-sectional one, our next step will be to evaluate these findings in a longitudinal study to analyze the changes in body composition, the appearance of fatigue, and the modifications in the skeletal muscle function. Our results add evidence about the relationships between body composition, weight loss, and parameters of skeletal muscle function; findings could be a theoretical support to understand sub-maximal strength and endurance as well as skeletal and fat mass with regard to tumor sites and percentage of weight loss.

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Compliance with ethical standards

The study protocol was approved by the Ethics Committee of the Bonorino Udaondo Gastroenerology Hospital of the city of Buenos Aires and met the recommendations stated in Helsinki Declaration. All the patients signed informed consent.

Conflict of interest The authors declare that they have conflict of interest.

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