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DIFFERENCES IN ANTHROPOMETRIC MEASURES BETWEEN CRITICAL LIMB THREATENING ISCHAEMIA AND INTERMITTENT CLAUDICATION IN PATIENTS UNDERGOING AORTO-BIFEMORAL BYPASS

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Abstract

Objective/Background: *Peripheral artery disease (PAD) is an important manifestation of systemic atherosclerosis. Obesity is a risk factor for atherosclerosis and for cardiovascular events. However, the relationship between obesity and PAD is unclear. We hypothesized that anthropometric measures of adiposity, in particularly of central obesity will be associated with PAD severity, in patients undergoing aorto-bifemoral bypass.*

Methods: *A prospective observation study was conducted. From 2009 and 2012 a total of 46 males who underwent aorto-bifemoral bypass were enrolled prospectively. 17 with intermittent claudication (IC) and 29 with chronic limb threatening ischemia (CLTI). They were followed for 5 years. The anthropometric measures, weight, body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and the seric levels of hemoglobin, triglycerides, and albumin were recorded. The mortality and cardiovascular events in following five years were also registered.*

Results: *The groups did not differ in the mean age (IC 60.69±7.46 versus CLTI 64.51 ±8.42 years, p=0.712), diabetes (IC 18% versus CLTI 45%, p=0.06), hypertension (IC 70% versus CLTI 52%, p=0.21), hypercholesterolemia (IC 18% versus CLTI 45%, p=0.47) and smoking habits prevalence (IC 100% versus CLTI 86%, p=0.11). The anthropometric measures: weight, WC and WHR were significant lower in CLTI compared to IC patients (IC 72.74±9.84 Kg versus CLTI 65.92±10.89 Kg, p=0.043; IC 98.65±8.19 cm versus CLTI 89.38±15.91 cm, p=0.017; IC 1.06±0.06 versus CLTI 1.01±0.06, p=0.038). The serum levels of hemoglobin, albumin and triglycerides were also lower in CLTI patients (IC 14,40±1.63g/dL versus CLTI 13.3±1.89g/dL, p=0.048; IC 4.6±0.81g/dL versus CLTI 4.3± 0.67g/dL, p=0.007; IC 212±95.60mg/Dl versus CLTI 111±41.53 mg/dL, p=0.001). No relation was found between the anthropometric measures at admission and the cardiovascular events or mortality at five years.*

Conclusion: *CLTI patients had lower anthropometric measures of obesity, when compared to IC patients. These results could be explained by the fact that CLTI patients with severe atherosclerotic disease are in a state of chronic inflammation, with consequent cardiometabolic demands and catabolism.*

INTRODUCTION

Peripheral artery disease (PAD) is an important manifestation of systemic atherosclerosis.[1,2,3] It is characterized by arterial stenosis and occlusion of arteries in the lower extremities.[1,2,3] PAD prevalence in adults is about 20% and affects 27 millions person in Europe and US.[3,4,5,6] Up to 44% of symptomatic patients have atherosclerosis in the aorta and iliac arteries.[3]

PAD coexists with other ischemic events.[3,4,7] The risk of myocardial infarction, stroke or cardiovascular death is substantially increased in patients with PAD.[1,3,7,8,9] Obesity is a risk factor for atherosclerosis, coronary heart disease, cardiovascular events and all-cause mortality.[10,11,12] However, the relationship between obesity and PAD is unclear.[10] It has been demonstrated that central obesity, but not generalized obesity is associated with PAD.[5] For others, PAD has been linked with a decreased body mass index (BMI) values, or no association was found.[3]

In a study conducted in patients with aortoiliac disease the authors concluded that waist–hip ratio (WHR) over 1.02 and percent of body fat over 26.5% are significant predictors of aortoiliac PAD, independent from blood pressure, cholesterol level and body mass index.

We hypothesized that anthropometric measures of adiposity, in particularly of central obesity, would be associated with PAD severity in patients submitted to aorto-bifemoral bypass. The aim of this study was to compare the anthropometric measures of IC versus CLTI patients, in subjects with indication for aorto-bifemoral bypass. The second objective was to analyze the relation between anthropometric measures at admission and the cardiovascular events and mortality in the following five years in this group of patients.

MATERIAL AND METHODS

Patients

• Inclusion criteria:

1. Male.
2. Aorto-iliac disease with indication to aorto-bifemoral bypass according to the decision of the Vascular Surgery department.

• Exclusion criteria:

1. Bedridden individuals.
2. Previous endovascular revascularization.
3. Other diseases that may be responsible for body composition changes or pro-inflammatory state: recent diet change, active malignancy, auto--immune disease, chronic renal failure (GFR <30 mL/min/1.73m2) or heart failure in the past 3 months.
4. Subjects who refused to participate in the protocol.

According to the inclusion and exclusion criteria, consecutive patients proposed to aorto-bifemoral bypass were included.

The study variables were collected at hospital admission before the surgical intervention, between 2009 and 2012. No clinical or interventional procedure was performed beyond what was already deemed the best treatment for the patient's condition.

Cardiovascular events and mortality occurring in the five following years were registered according to the Portuguese government database Sclinico. All the records were collected by one operator.

Ethical considerations

Ethics approval for data collection and cohort evaluation were obtained from the Ethics Committee of the local Hospital. The study was conducted according to Helsinki declaration, national and European guidelines for clinical research. The confidentiality of clinical records was assured for both patients' information and processing of biological samples. All the participants signed the informed consent.

Determined variables

• Clinical characteristics at admission

Patients' age, co-morbidities and medication taken at admission were recorded. Arterial hypertension was defined as requiring treatment with oral antihypertensive agents or as systolic blood pressure ≥ 140 mmHg and/or diastolic ≥ 90 mmHg. Diabetes was considered if the patient was taking anti-diabetic medications, fasting glycaemia ≥126 mg/dL, or glycated haemoglobin (HbA1c) ≥ 6.5%. The diagnosis of dyslipidemia was described as requiring treatment with statins or a low density lipoprotein (LDL) ≥ 130 mg/dL, total cholesterol ≥ 200 mg/dL or plasma triglycerides ≥ 200 mg/dL. The smoking habits were classified as active smoker, former smoker or non-smokers and quantified in pack-years (multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked). Former smoker was defined as smoking cessation for at least six months.

CLTI was defined as ischemic rest pain or tissue loss (ulceration or gangrene). Ischemic rest pain was considered if the patient describes pain for more than for >2 weeks, affecting the forefoot, worse with recumbency, relieved by dependency and with an ankle pressure less than 40-50 mmHg (not valorized in the presence of medial calcinosis). Tissue loss to CLTI includes gangrene of any part of the foot or nonhealing ulceration and with an ankle pressure less than 50-70 mmHg (not valorized in the presence of medial calcinosis).

• Cardiovascular events and mortality five years later

Hospital mortality of any cause, hospital admission for carotid endarterectomy, stroke, angina and myocardial infarction were recorded in the following five years.

Anthropometric measurements

The measurements were taken after 5 minutes of rest in a comfortable room. The subjects' height and weight were measured while they wore indoor clothes and no shoes. BMI was calculated dividing the weight by height squared (kg/m^2). Waist circumference (WC) was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest in the horizontal position, using the anthropometric tape. The hip circumference measurement was taken around the widest portion of the buttocks. WHR was calculated as waist circumference divided by hip circumference. Ankle brachial index (ABI) was determine with a handheld Doppler and an aneroid sphygmomanometer manual blood pressure. The measurements taken were the systolic pressure at the brachial artery, anterior tibial artery, posterior tibial artery and peroneal artery. Three measures in each point were recorded in each arm and foot. The ankle brachial index was calculated for each leg as the ratio of the higher systolic pressure in the ankle by the higher systolic pressure in the arm. The blood pressure was determined with the patient seated. Three measurements, spaced 2 min apart, was recorded with an electronic sphygmomanometer in both upper limbs, using an appropriate cuff size for arm circumference.

Fasting blood was sampled to ascertain levels of hemoglobin, glucose, glycosylated hemoglobin A1c, total cholesterol, HDL-cholesterol, triglycerides, creatinine, albumin. All assessments were performed by a single laboratory.

Statistical analysis

Results are expressed as means with standard deviations or as percentages unless otherwise stated. Continuous variables were compared using the Student t test. The X2 test was used to compare the prevalence of categorical data. P <0.05 was considered statistically significant for all test.

RESULTS

168 patients were proposed to aorto-bifemoral bypass during the study period. 46 patients (all males) fill the inclusion criteria: 17 with IC and 29 with CLTI (Figure 1). Demographic characteristics of subjects are presented in Table 1. The groups did not differ in the average age, diabetes, hypertension, total cholesterol and smoking habits prevalence. However, the CLTI group had a lower prevalence of patients with hypertriglyceridemia (CLTI 6% versus IC 53%, p=0.039). ABI of the studied population was 0.346±0.23 (0.45±0.17 for IC and 0.27±0.23 for CLTI, p=0.0085). At admission CLTI patients were less like

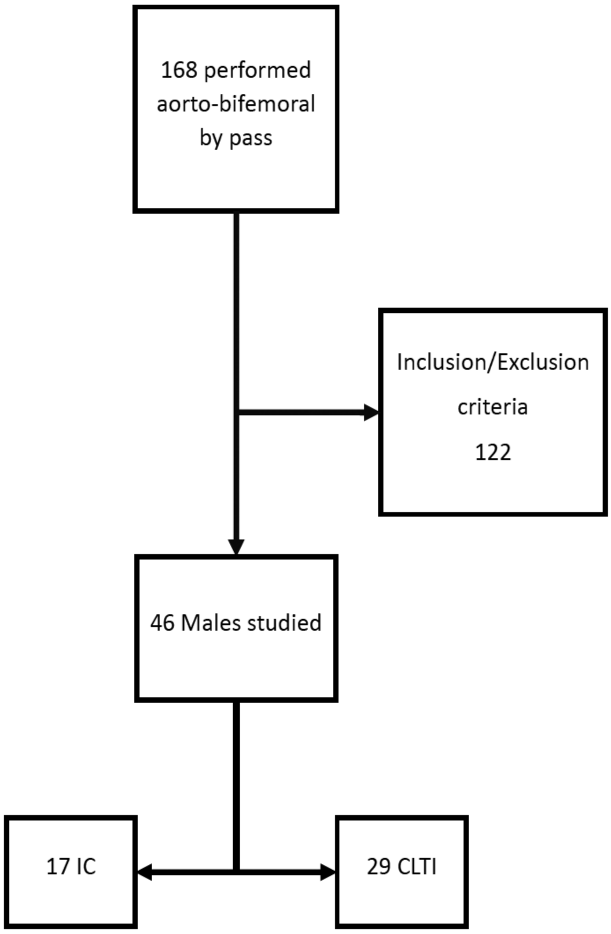

Figure 1 *Patients fluxogram.*

Table 1 **Characterization of the population according to PAD severity. Characterization of IC and CLTI study groups according to the age, prevalence of hypertension, diabetes, smoking habits and number of patients with hypertriglyceridemia, hypercholesterolemia, taking antiplatelets and statins. The difference in ABI index is also shown.**

	IC (n=17)	CLTI (n=29)	P value
Age (years), mean ± SD	60.69 ±7.46	64.51 ±8.42	p=0.712
Hypertension, %	70.00	51.72	0.21
Diabetes, %	17.60	44.80	0.06
Smoker/Ex-smoker, %	100.00	86.20	0.11
Hypertriglyceridemia, %	53.33	5.88	0.039*
Hypercholesterolemia, %	33.33	22.22	0.47
Antiplatelet, %	82.35	41.38	0.0001
Statins, %	64.70	37.93	0.079
ABI, mean ± SD	0.45±0.17	0,27±0.23	0.0085*

P values denotes the results from the Student t test and form the X2 test as appropriate. *P <0.05 was considered statistically significant for all test.
Abbreviation: Antiplatelet- Taking antiplatelet at hospital admission. Statins- Taking statins at hospital admission. ABI- Ankle-brachial index. SD – Standard deviation.

Table 2 **Distribution of the anthropometric measures and serum measurements, according to PAD severity**

	IC (n=17)	CLTI (n=29)	P value
BMI (Kg/m2)	25.10±5.01	23.52±3.59	0.27
Weight (Kg)	72.74±9.84	65.92±10.89	0.043*
WC (cm)	98.65±8.19	89.38±15.91	0.017*
WHR	1.06±0.06	1.01±0.06	0.038*
Hb (g/dL)	14.40±1.63	13.3±1.89	0.048*
Platelets	234.53±63.70	267.67±103.77	0.20
Leucocytes	7.75±1.87	8.23±2.89	0.56
NLR	2.98±2.07	2.55±1.57	0.44
Albumin (g/dL)	4.60±0.81	4.30± 0.67	0.007*
Triglycerides (mg/dL)	212±95.60	111±41.53	0.001*

Values presented correspond to mean ±standard deviation. P values denotes the results from the Student t test. * P <0.05 was considered statistically significant for all tests.
Abbreviation: BMI- body mass index, WC-waist circumference, WHR- waist hip ratio, Hb- hemoglobin, NLR- neutrophil-lymphocyte ratio.

Table 3 **Relation between anthropometric measures and cardiovascular events and mortality at 5 years. Hospital admission due to angina, myocardial infarction, ischemic and haemorrhagic stroke, carotid endarterectomy and mortality were recorded in the following 5 years after the admission to perform aorto-bifemoral bypass.**

	BMI (Kg/m^2)	Weight (Kg)	WC (cm)	WHR
CAD	27.86±2.01	80.5±10.47	107.5±6.05	1.05±0.05
Non-CAD	23.78±4.27	67.69±10.53	92±14.09	1.03±0.44
P value	0.069	0.058	0.074	0.285
Stroke	20.59±3.12	56.78±2.51	84±8.48	0.94±0.05
Non-stroke	25.05±4.27	70.00±10.80	95±14.17	1.04±0.06
P value	0.225	0.120	0.357	0.235
Carotid endarterectomy	27.61±11.05	77±10.54	92±11.93	1.03±0.10
Non-carotid endarterectomy	24.44±3.55	70.00±10.76	94.5±14.48	1.04±0.06
P value	0.436	0.130	0.740	0.940
Mortality	27.61±11.05	77±10.54	92±11.93	1.03±0.10
Non-Mortality	24.44±4.36	70.00±10.93	94.0±14.69	1.03±0.07
P value	0.550	0.618	0.807	0.623

Values presented correspond to mean ±standard deviation. P values denotes the results from the Student t test. * P <0.05 was considered statistically significant for all tests.
Abbreviation: CAD- coronary heart disease; carotid endarterectomy- patient submitted to carotid endarterectomy; BMI- body mass index, WC-waist circumference, WHR- waist hip ratio.

to be taking antiplatelets, as well as statins. The Table 2 shows the anthropometric measures and serum evaluations in the two groups. The weight, WC, WHR and the serum levels of hemoglobin, albumin and triglycerides were significant lower in CLTI compared to IC patients. No difference was found between the groups about platelets, leucocytes and neutrophil-lymphocyte ratio (NLR) levels. No relation was found between the anthropometric measures and the cardiovascular events or mortality at 5 years (Table 3).

DISCUSSION

Our hypothesis was not demonstrated. We hypothesized that anthropometric measures of adiposity, in particularly of central obesity would be associated with PAD severity, in patients with aorto-iliac disease undergoing aorto-bifemoral bypass. |Instead we found that BMI, weight, WC, WHR were lower in CLTI patients when compared to IC, in this sample. Patients with a more severe form of atherosclerosis had lower anthropometric measurements, including those associated with visceral obesity (WC, WHR).

Our initial hypothesis was based on the fact that obesity promotes endothelial dysfunction, systemic inflammation, and a prothrombotic state, having a role in atherosclerosis.[2,12] BMI and weight are a measure of overall fatness.[7] However, BMI and weight do not estimate body composition, do not provide information about the distribution of fat and cannot distinguish between lean and fat mass.[3,4,7] WC and WHR are measures of abdominal/ visceral obesity and are associated with cardiovascular morbidity and mortality, including stroke, congestive heart failure, myocardial infarction cardiovascular death and PAD.[2,7,10,13,14,15] Visceral adipose tissue is the most metabolically active fat store, producing pro-atherogenic and inflammatory mediators and reducing the secretion of vascular-protective adipokines.[4,14,15,16,17] Abdominal obesity is related to metabolic changes, such as dyslipidemia, type 2 diabetes mellitus, hypertension, inflammation, oxidative stress and hypercoagulability, which are all associated with an increased cardiovascular risk.[14,18] Obesity, particularly abdominal adiposity is associated with PAD severity.[14,19]

The two groups analyzed in this study were both proposed for aorto-iliac revascularization and were relatively homogenous, in the distribution of cardiovascular risk factor (except triglycerides) and age. The groups differ in ABI, as expected.

In this study, weight, WC, WHR were significant lower in CLTI patients when compared to IC. These results agree with a previous study in aortoiliac PAD patients (only one), that showed that all anthropometric parameters (BMI, WC, WHR) strongly inverse correlated with ABI.[3]

In severe atherosclerotic disease, there is a state of chronic inflammation, with a higher cardiometabolic demands and consequently lower body fatness.[20,21] CLTI patients have a reduction in their mobility with muscle atrophy and consequently lower mean mass[18]. These changes are associated with low albumin, nutritional dysfunction and immunity compromise.[20] In this study, we found lower seric levels of albumin, triglycerides and hemoglobin in CLTI group (and these differences were statistically significant between the groups). In fact, the literature reports that BMI also had significant positive correlations with triglyceride and albumin.[9] Shah also reported that anemia and malnutrition are common in CLTI patients.[22] CLTI patients also suffer from chronic inflammation, ulceration and gangrene that contribute to chronic anaemia.[22] Salomom realized that in 106 patient with CLTI, the prevalence of malnutrition was 75.5%.[23] Due to this data the management of PAD patients includes the evaluation of the patient nutritional status and prevention of protein waste.[21]

We did not find any differences in platelets or leucocytes count or neutrophil-lymphocyte ratio (NLR) between the groups. We would expect increased leucocytes in CLTI patients, as reported by other authors, due to an increased in inflammation, endothelial damage, procoagulant effect and microvascular damage.[24] It was also described that NLR is significantly associated with the presence of CLTI in 2121 patients with PAD.[25]

We noted that CLTI patients were less likely to be taking antiplatelets as well as statins. These differences could be explained by the fact that IC patients were already followed by a vascular surgeon before the hospital admission. The majority of CLTI were admitted from the emergency room and were not properly medicated.

In this study there was no association between anthropometric data and the incidence of stroke, carotid endarterectomy, coronary heart disease and mortality. The lack of results could be explained by the sample size and by the fact that just hospital data was taken in account. In the literature, the association between anthropometric measures of obesity and cardiovascular events in PAD patients is controversial. Kumakura demonstrated that low BMI is risk factor for mortality in PAD patients.[9] Murata proved that, in CLTI patients who underwent endovascular therapy, the low weight was related with poorer prognosis at 3 years.[9,26] Some authors showed that abdominal obesity is a strongly predictor of cardiovascular events.[4,27] Cronin and other authors did not find an association between visceral adipose volume and cardiovascular events in the PAD population.[18,27]

LIMITATIONS

The sample size is small. The anthropometric measures do not rigorously determine the body composition, which would be better determined with a CT scan or MRI. The study cannot be applied to atherosclerotic disease in other anatomic locations, because it is limited to PAD patients with aorto-iliac disease. The inclusion of surgical patients may introduce bias. BMI increases the risk of postoperative surgical site infections, pneumonia and prolonged ventilation. The surgeons tend to propose obese patients to endovascular repair. The anthropometric measures were determined at baseline and could have changed during follow-up. Dietary habits, alcohol consumption, physical activity were not determined.

CONCLUSION

In this small series of patients who underwent aorto-bifemoral bypass, the CLTI had lower anthropometric measures of obesity (BMI, weight, WC, WHR), when compared to IC patients. There is no association between the anthropometric data at admission and the incidence of stroke, carotid endarterectomy, coronary heart disease and mortality. Further studies are needed to corroborate this data. However, this study calls attention to importance of the metabolic optimization of the PAD patients.

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