

# Subclinical Atherosclerosis at Peripheral Arteries in Obese Individuals

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**Abstract.** Evidence on relationship between obesity and peripheral arterial disease (PAD) are controversial. The aim of the present study is to evaluate the presence of subclinical atherosclerosis at all level of the explorable vascular segments with a systematic method in a selected population of young obese submitted to a comprehensive rehabilitation course. A group of 50 consecutive morbidly obese (BMI>30) was included. All patients underwent Doppler evaluation including intima media thickness (IMT) and presence/absence of plaques.

**Results.** We found that vessels in the upper segment of the body demonstrate the presence of thickening and/or plaques at the level of the carotid segments but not of the subclavian arteries. The IMT of the right Common Carotid Artery (CCA) (1.49 + 1.38 versus 0.62 + 0.23; p=0.037) and of the left CCA (1.66 + 1.89 versus 0.45 + 0.26; p=0.034) was greater in patients. Vessels of the lower segment demonstrate the presence of thickening and/or plaques at the iliac but not at femoral level. The control group did not present vessel thickening at any level. In conclusions asymptomatic vascular damage may be present in different segment of peripheral vessels, thus suggesting an early risk for developing an overt vascular disease over time in obese.

**Key words:** obesity; peripheral arterial disease; intima/media thickness

## Background

Obesity is a global epidemic, affecting an increasing proportion of the world's population [1]. In 2014, approximately 40% of adults worldwide were estimated to be overweight, and 13% obese according to the definition of a body mass index (BMI)  $\geq 30$  [2]. Conflicting reports in the literature have found different types of negative, positive or non-associations between obesity and peripheral arterial disease (PAD) [3, 4, 5].

The cornerstone of preventative public health is based on fighting the progression of any asymptomatic condition into a full clinical state. For this purpose, the association of obesity and asymptomatic PAD as a subclinical marker of atherosclerosis and predictor of cardiovascular events has been evaluated in population-based studies [6, 7].

The prevalence of asymptomatic PAD continuously rises by the advancing age, estimated to affect 3% of the general population <60 years old and as high

as 15–20% of people aged above 70 years. A previous estimate from an observational study of asymptomatic PAD reported a rate of 15.6% in women and 13.4% in men [8, 9, 10].

The present study aims to evaluate the presence of subclinical atherosclerosis at all level of the vascular segments explorable with a systematic method in a selected population of young obese submitted to a comprehensive rehabilitation course but without evidence of overt clinical cardiovascular disease(s).

## Methods

A group of 50 consecutive morbidly obese (BMI >30) was included. Patients were selected among those admitted to a comprehensive course of rehabilitation, including exercise and diet as previously described [11], delivered as outpatient at the facility of Villa Pineta Hospital (Pavullo nel Frignano, Modena-I) in the period may-nov 2018. Selected population was then referred to our clinic at the Department CHIMOMO of the University of Modena and Reggio Emilia (Modena-I) for screening and prevention of PAD and had complete non invasive vascular evaluation (see below).

Patients were included only if they were free of symptoms of PAD. Therefore, we have excluded obese with a previous history of cardiovascular disease, (ischemic heart disease, heart failure and stroke), and those who did not undergo vascular evaluation and who did not sign the consent. The group of patients that completed the peripheral vascular evaluation included 32 obese subjects (mean BMI 34.9 + 6.67, range 34.9- 60.1). Data were compared with a control group that included 10 age and sex-matched healthy individuals (mean BMI 21.76 + 1.9, range 16.9-24).

Study was approved by the Institutional Review Board and participants signed an informed consent.

### *General data collection.*

Anthropometry, general status, risk factors and pathological conditions, serum blood analysis, and drug therapies were recorded by chart records and interview. Nutritional status was assessed by measuring

weight, body mass index (BMI), waist circumference and waist-to-hip ratio. [11]

### *Vascular examination*

All patients underwent peripheral vascular measurement. For these analyses we used a non-invasive Doppler ultrasound in order to obtain the best results. [12]

The following arteries were evaluated: common carotid arteries (CCA); internal carotid arteries (ICA); subclavian arteries (SA); common iliac arteries (CIA); femoral arteries (FA).

Measures of intima/media thickness (IMT) and plaque were obtained. The IMT was measured by trained readers and was assessed in 3 segments: the distal common carotid (1 cm proximal to dilation of the carotid bulb), the carotid artery bifurcation (1 cm proximal to the flow divider), and the proximal internal carotid arteries (1 cm section of the internal carotid artery immediately distal to the flow divider). At each of these segments, 3 measurements of the far wall (in 1-mm increments) were attempted.

The mean of the 3 measurements across these segments of both the right and the left sides was estimated.

Trained readers adjudicated plaque presence or absence if 2 of the following 3 criteria were met: abnormal wall thickness (defined as > 1.5 mm), abnormal shape (protrusion into the lumen, loss of alignment with adjacent arterial wall boundary), and abnormal wall texture (brighter echoes than adjacent boundaries) [13]

Evaluation of the flow in the distal CIA with an echocardiographic probe was performed. The patients were placed in the supine position and the IA were localized in the inguinal area, first with the two-dimensional, and then with the color Doppler imaging.

The femoral IMT was defined, as in prior studies, as the combined thickness of the intima and media layers, from the leading edge of the intima-lumen border to the leading edge of the media-adventitia border [14]

The ABI is a simple, noninvasive test, measuring the systemic blood pressure (SBP) from both brachial arteries and from both the dorsalis pedis and posterior tibial arteries after the patient has been at rest in the supine position for 10 min by using a Doppler

device. The ABI of each leg is calculated by dividing the higher of the dorsalis pedis pressure or posterior tibial pressure by the higher of the right or left arm blood pressure. [15]

### Statistical analysis.

SPSS package, V.21.0.1 (SPSS Inc, Chicago, Ill) was used for statistical analysis. Results are presented as mean + SD or frequency expressed as a percentage.

Before group comparison, we first adjusted for age, sex and adherence to Mediterranean Diet, and additionally for total cholesterol, HDL cholesterol, systolic blood pressure.

## Results

Characteristics of patients and controls are shown in table 1. As expected cardiovascular risk factors were significantly more frequent in obese. Total serum cholesterol (210 + 33 vs 179 + 11 mg/dl;  $p < 0.05$ ) and uric acid (6 + 1 vs 3 + 0.7 mg/dl;  $p < 0.001$ ) were increased in patients group. On the contrary, triglycerides were higher in controls (161 + 78 vs 171 + 10 mg/dl;  $p$  trend to  $< 0.05$ ).

Adherence to Mediterranean Diet evaluated as Mediterranean Score was higher in control group (mean Med Score: 20.3 + 2.4 vs 30.9 + 5.2;  $p < 0.001$ ). The median value was 19.5 (Q1-Q3 range 18-30) in obese patients and 27.7 (Q1-Q3 range 23-36) in controls.

Distribution of waist circumference and glycemic assets among obese patients are shown in fig 1 and 2, respectively.

The ABI was significantly lower in patients compared to control (0.91 + 0.02 vs 1 + 0.01;  $p < 0.05$ )

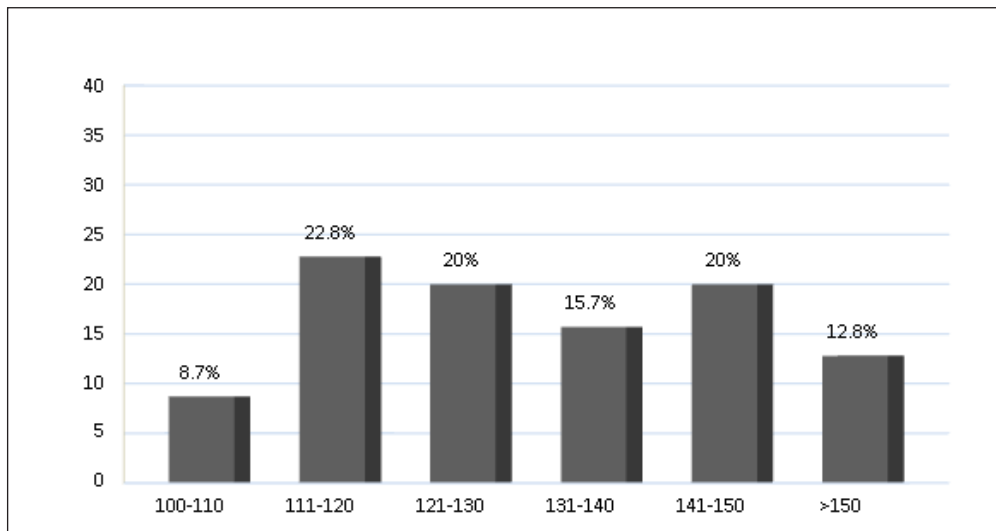
The peripheral vascular parameters are displayed in table 2.

When comparing the peripheral vascular parameters we found that the IMT of the right CCA (1.49 + 1.38 versus 0.62 + 0.23;  $p = 0.037$ ) and of the left CCA (1.66 + 1.89 versus 0.45 + 0.26;  $p = 0.034$ ) was greater in patients than in controls. The IMT of the right SA was altered in obese (0.47 + 0.82) compared to controls who showed no lesion(s).

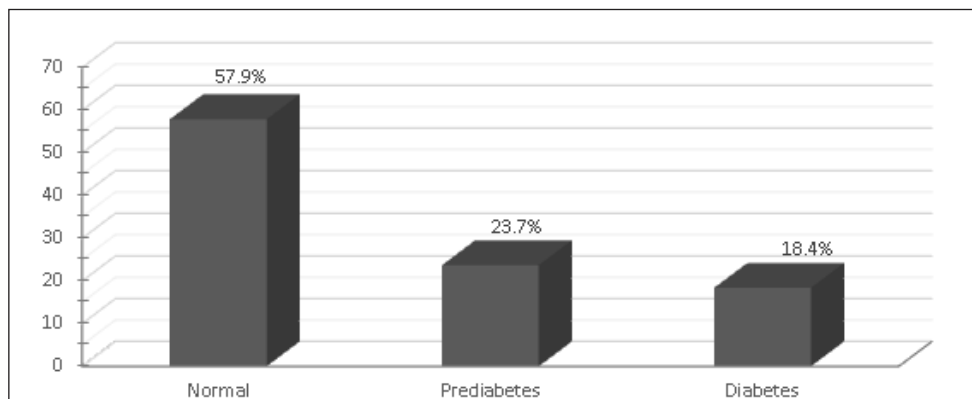
**Table 1** Clinical characteristics and cardiovascular risk factors in total population

	Patients	Controls	p
Sex (F/M)	22/10	6/4	
BMI	44.9 + 6.6	21.7 + 1.9	< 0.001
Waist Circumference	133.8 + 14.6	89.3 + 6.0	< 0.001
Hb	13.1 + 1.6	13.0 + 0.7	n.s.
Ht	39.1 + 4.5	41.6 + 3.8	n.s.
Clo tot	210 + 33	179 + 11	< 0.05
Trig	161 + 78	171 + 10	n.s.
GLic	101 + 36.9	91 + 7	n.s.
GOT	26 + 26	29 + 10	n.s.
GPT	35 + 5.2	30 + 5.4	n.s.
Uric acid	6 + 1	3 + 0.7	< 0.001
Creatinine	0.94 + 0.25	0.96 + 0.13	n.s.
Urea	35 + 11	34 + 4	n.s.
<b>CV risk factors</b>			
diabetes	12 (37.5%)	0	0.04
hypertension	7 (21.8%)	0	0.024
Actual smoking	8 (25%)	2 (16.6%)	0.045
Familiar history of CVD	20 (62.5)	5 (41.6)	0.014
Familiar History of obesity	12 (37.5%)	2 (16.6)	0.0001
alcohol	8 (25%)	0	0.014
<b>Therapy</b>	patients	controls	p
Statins	4 (12.5%)	0	
Antiplatelets	3 (9.3%)	0	
Anticoagulants	3 (9.3%)	0	
Diuretics	12 (37.5%)	0	
ACE inhibitors	8 (25%)	0	
Beta-blockers	7 (21.8%)	0	
Ca Antagonist	6 (18.75%)	0	
Anti diabetic therapy	6 (18.75%)	0	

The assessment of the lower extremity artery disease demonstrated that the CIA was significantly damaged in obese patients compared to healthy individuals both at the right (1.97 + 1.67 versus 0.65 + 0.57;  $p = 0.011$ ) and the left (2.42 + 2.39 versus 0.55 + 0.61;  $p = 0.011$ ) sides (see in table 2).



**Fig. 1** Distribution of waist circumference among obese patients



**Fig. 2** Glycemic assets in patients population

## Discussion

The major result of the present study is the likely existence of subclinical peripheral arterial disease in young obese subjects.

As far as our knowledge, no previous study has comparatively analysed the presence of subclinical atherosclerosis at all level of the vascular segments explorable with a systematic and homogeneous method.

The results of the evaluation of vessels in the upper segment of the body demonstrate the presence of thickening and/or plaques at the level of the carotid segments but not of the subclavian arteries.

The evaluation of the vessels of the lower segment demonstrates the presence of thickening and/or plaques at the iliac but not at femoral level. The control group did not present vessel thickening at any level.

Overall, these findings suggest that asymptomatic vascular damage may be present in different peripheral vessels, thus suggesting an early risk for developing an overt vascular disease over time in obese individuals. The common risk factor in the subjects studied is the presence of morbid obesity. Few studies have investigated the association of body mass index (BMI) with quantitative measures of carotid plaque, although they failed to demonstrate any significant association [16, 17].

**Table 2** Non invasive ultrasound doppler parameters in peripheral vessels

	Patients	Controls	p
CCA Dx	1.4 + 1.3	0.6 + 0.2	0.037
ICA Dx	0.73 + 0.67	0.46 + 0.42	n.s.
CCA Sx	1.6 + 1.8	0.45 + 0.26	0.034
ICA Sx	0.66 + 0.87	0.25 + 0.32	n.s.
SA Dx	0.47 + 0.82	0.00 + 0.00	0.057 (trend to)
SA Sx	0.19 + 0.47	0.00 + 0.00	n.s.
CIA Dx	1.9 + 1.6	0.6 + 0.5	0.01
CIA Sx	2.4 + 2.3	0.5 + 0.6	0.01
FA Dx	0.7 + 1.3	0.4 + 0.4	n.s.
FA Sx	0.8 + 1.6	0.3 + 0.4	n.s.

Legend: common carotid arteries (CCA); internal carotid arteries (ICA); subclavian arteries (SA); common iliac arteries (CIA); femoral arteries (FA)

Previous studies have largely reported positive associations between central obesity and its variant substitutes including periaortic fat content, but not general obesity phenotype, with the presence of PAD (thus, negative correlations with ABI); though the association between BMI with PAD is less clear [18,19, 20, 21,22].

Notwithstanding, the value of BMI as a surrogate of obesity presents limitations: indeed, it doesn't reflect body fat distribution nor differentiate between fat and lean mass. In addition, a body of recent clinical evidence shows that a substantial residual cardiovascular risk exists even at very low levels of LDL-C, suggesting that new therapeutic modalities are still needed for reduction of atherosclerosis morbidity and mortality. [23,24] Recent studies suggest that abdominal obesity may be correlated with CVD risks more strongly than general obesity. [19,20]

Addison and colleagues explored self-reported body-weight trends and methods used to achieve weight loss in patients with PAD included in the 1999-2004 National Health and Nutrition Examination Survey (NHANES) [25].

They found that individuals with PAD and controls reported similar weights 10 years prior (79.2 kg vs 78.5 kg;  $p = 0.60$ ) and weight gain over the last 10 years of 5.7 kg. There was no significant difference in reported body weight at age 25 years, 10 years prior,

1-year prior, or heaviest weight. Compared with the control group, fewer participants with PAD reported attempted weight loss in the last year (27.50% vs 36.04%;  $p = 0.02$ ) and were half as likely to report utilizing exercise as a weight-loss method (12.5% vs 21.7%;  $p = 0.003$ ) [26].

Tanaka and colleagues supports that obesity by itself is not a risk factor for reintervention and was a protective factor for mortality after open aortoiliac bypass surgery (the *obesity paradox*). Bypass graft patency and major amputation rates were not affected. Although the individual components do not predispose to worse outcome, metabolic syndrome is a constellation of factors that, taken together, are associated with adverse events. [27, 28]

Haberka and colleagues found that obese patients with BMI  $\geq 30$  had similar ultrasound carotid artery stenosis parameters compared to individuals with lower BMI. In addition, neither BMI nor BF% was associated with any CAS measures, including: the maximum or mean severity of carotid stenosis or atherosclerotic plaque burden. Although obesity is a cardiovascular risk factor, our results suggesting no relationship with CAS are in line with previous reports [29].

### Limitation of the study

The major limitation of the present study is the distribution of patients within BMI categories that lead to a little number of patients in each category. Even if the great majority of patients had a BMI greater than 35.

In addition, this cross sectional study lacks in follow up and follow back

### Conclusion

In conclusion obesity is a strong risk factor for asymptomatic atherosclerosis. Our results suggest that non invasive evaluation of peripheral vessels is a useful screening for asymptomatic atherosclerosis in obese.

Further studies are needed in order to confirm these results and to suggest strategy for early diagnosis of preclinical atherosclerosis.

## Authors' contributions

A.F., E.C. and A.V.M. conceived of the idea at the basis of the article, A.F., E.C., A.G, F.S, R.G., I.C. and F.Sp evaluated patients and performed clinical study, F.S.R and N.A. evaluated nutritional status, A.V.M. and A.F. contributed to writing the article; all authors contributed to the critical review of the article.

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## Conflict of interest

All authors declare no conflict of interest.

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