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Carotid intima media-thickness is increased in obese children metabolically healthy, metabolically unhealthy, and with metabolic syndrome, compared to the non-obese controls

G. FARELLO[1], G. IAPADRE[2], M. LIZZI[2], C. GENTILE[2], E. ALTOBELLI[3], F. CIOCCA[4], A. VERROTTI[2]

[1]Department of Life, Health and Environmental Sciences – Pediatric Unit – University of L'Aquila, L'Aquila, Italy
[2]Department of Pediatrics, University of L'Aquila, L'Aquila, Italy
[3]Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy
[4]Vascular Surgery Unit "San Salvatore Hospital" L'Aquila, Italy

Abstract. – The prevalence of obesity continues to increase. Obesity is associated with cardiovascular risk factors: elevated blood pressure, dyslipidemia and glycemic alterations, causing metabolic syndrome. A subgroup of obese, Metabolically Healthy Obese (MHO), appears to be less prone to the development of metabolic disturbances. Carotid intima-media thickness (cIMT) is a non-invasive marker of subclinical atherosclerosis and it is associated with increased risk of CVD events. To investigate the cardiovascular risk, demonstrated through the increase of cIMT in obese subjects without Metabolic Syndrome (MetS), we have studied cIMT in MHO, metabolically unhealthy obese (MUO) and obese with MetS diagnosed with the IDEFICS criteria and compared to a control group.

224 obese children aged 6 to 21 years (13,50 +/- 4.01 years) and 103 normal weight subjects aged 7 to 19 years (13.2 +/- 4.1 years) were studied. The body mass index (BMI) of the obese children was ≥ the 95th percentile.

Based on the IDEFICS criteria, we divided the obese subjects in three groups: MHO if no criteria were out of range, MUO if, at least, one of the criteria was out of range and MetS group if all the IDEFICS criteria were present.

In all the subjects cIMT was measured with color Doppler by a vascular surgeon. Differences in the means of the variables were tested by ANOVA.

Based on the IDEFICS criteria, 32 subjects were affected by MetS (14,3%), 66 were considered MUO (29,4%) and 126 MHO (56,3%).

Comparison of mean cIMT highlighted a significant difference ($p < 0.05$) between the groups of obese children (MHO, MUO and MetS) and controls for both carotid arteries.

We did not find significative difference in the value of cIMT in MHO, MUO and MetS subjects, and all groups showed cIMT value higher compared to cIMT of the controls.

Key Words:
Carotid intima media thikness (cIMT); Metabolic syndrome (Met.S), Metabolically health obese (MHO), Metabolicallu unhealthy obese (MUO), Insulin resistence (IR), Cardiovascular risk (CR), IDEFICS, Children obesity.

Abbreviations

cIMT: carotid Intima Media Thickness; MUO: Metabolically Unhealthy Obese; MHO: Metabolically Healthy Obese; MetS: Metabolic Syndrome; CVD: Cardio Vascular Disease; IDEFICS: Identification and prevention of Dietary - and lifestyle - induced health Effects In Children and infantS; IDF: International Diabetes Federation.

Introduction

The prevalence of obesity in youth continues to increase, and so does the frequency of obesity-related comorbidities. According to the Global Health Observatory Data 2017 by World Health Organization (WHO), there are over 340 million obese children and adolescents aged 5-19[1].

In Italy, about 21% of children are overweight and 9% are obese[2] with obesity trends expected to further increase[3].

It has been shown that both physical and psychosocial complications of obesity are present in childhood and worsen in adulthood[4].

Corresponding Author: Giovanni Farello, MD; email: giovanni.farello@cc.univaq.it

Obesity is associated with cardiovascular risk factors, including elevated blood pressure (BP), dyslipidemia and glycemic control alterations, causing Metabolic Syndrome (MetS).

MetS is defined by combination of dyslipidemia, abnormal glucose regulation, central adiposity and hypertension that directly increase the risk of cardiovascular disease (CVD) events.

Since its first definition by Reaven in 1988[5], many international organizations and expert groups have attempted to propose a validated definition of MetS in adults and children[6-13] (Table I).

In 2007, the International Diabetes Federation (IDF) provided a definition for MetS in the pediatric population using pediatric specific criteria[7].

In 2014 consortium IDEFICS (Identification and prevention of Dietary – and lifestyle – induced health Effects in Children and infantS) estimated the prevalence of the MetS using reference standards obtained in European children based on the following criteria: Waist Circumference (WC) ≥90th percentile, Systolic Blood Pressure (SBP) ≥90th percentile or Diastolic Blood Pressure (DBP) ≥90th percentile, Triglycerides ≥90th percentile or HDL cholesterol ≤10th percentile, HOMA-insulin resistance ≥90th percentile or fasting glucose ≥90th percentile[9].

The prevalence of MetS in childhood and adolescence has been estimated to differ between 6 and 39%, depending on which diagnostic criteria are applied[14].

Evidence[15,16] demonstrate that not all obese children show typical alterations of Mets.

A subgroup of obese youths, called "Metabolically Healthy Obese" (MHO), appears to be less prone to the development of metabolic disturbances and seems to display a "favorable" metabolic state[17-19].

The prevalence of MHO in children varies from 3 to 87%, depending on the definition used and the parameters evaluated[20].

The first consensus-based definition of pediatric MHO was introduced in 2018 by Damanhoury et al[19] and was based on the cut-offs values provided by the IDF definition of MetS in youth. In respect to this definition, only children with obesity fulfilling all the cardiometabolic criteria shown in Table II should be classified as MHO.

Recently, it was described the "Metabolically Unhealthy Obese" phenotype (MUO), defined as an obese subgroup characterized by alteration of one or more of MetS typical parameters[21] and, consequently, by a higher cardiovascular risk.

Carotid intima-media thickness (cIMT) is a non-invasive marker of subclinical atherosclerosis[22], obtained from ultrasonography and it is associated with increased risk of CVD events[23-25]. Increased cIMT in adults has been significantly associated with cardiovascular comorbidities[26]. Previous evidence[27] has shown increased cIMT both in MHO and MUO obese children compared with normal weight children.

So far, the association between MetS and cIMT in pediatric populations, has been examined only by few studies[28-30].

The increasing worldwide prevalence of childhood obesity have highlighted the importance of identifying children and adolescents with multiple cardio-metabolic risk factors.

In order to investigate the cardiovascular risk in obese subjects, we have studied the value of cIMT in a population of MHO, MUO and obese with MetS diagnosed with the IDEFICS criteria compared to a control group.

Patients and Methods

Subjects

Participants were 224 obese children (103 F and 121 M) aged 6 to 21 years (13,50 +/- 4.01 years); 103 normal weight subjects (49 F and 54 M) aged 7 to 19 years (13.2 +/- 4.1 years) represent the control group. The body mass index (BMI) of the obese children was ≥ the 95th percentile, whereas the BMI of control children was between the 25th and the 75th percentile[31]. Participants were recruited at the Pediatric Clinic of the University of L'Aquila – Auxology service. Exclusion criteria were secondary obesity, other syndromes, and use of medications known to alter blood pressure or lipid or glucose metabolism. We studied only the subject with primary obesity in order to avoid confusing factors. Based on the IDEFICS criteria, we divided the obese subjects in three groups: MHO if WC > 90 centile, Triglycerides < 90 centile (age and sex specific), HDL-C > 10 centile (age and sex specific), SBP/DBP < 90 centile (age, sex and height specific), HOMA-IR or FPG < 90 centile (age and sex specific); MUO if at least one of the criteria was out of range and to the MetS group if all the IDEFICS criteria were present. For the evaluation of the reference value for age and sex of the centile of triglycerides, HDL cholesterol, fasting glucose and insulin we used the data published by Mellerio et al[32]. The Pediatric Department Ethical Committee approved the study (protocol number 21/2020).

Table I. MetS diagnostic criteria.

Definition		Obesity	Blood pressure	Blood lipids		Blood glucose
Cook et al (6)	Three or more factors	WC ≥ 90th percentile (age and sex specific)	SBP/DBP ≥ 90th percentile (age, sex and)height specific	TG ≥ 1.24 mmol/L	HDL-C ≤ 1.03 mmol/L	FPG ≥ 6.1 mmol/L
IDF (7)	Central obesity plus any two of the other four factors	WC ≥ 90th percentile (age and sex specific) or adult cut-off if lower	SBP/DBP ≥ 130/ 85 mmHg	TG ≥ 1.7 mmol/L	HDL-C < 1.03 mmol/L	FPG ≥ 5.6 mmol/L
China (8)	Central obesity plus any two of the other four factors	WC ≥ 90th percentile (age and sex specific)	SBP/DBP ≥ 95th percentile (age, sex and height specific)	TG ≥ 1.47 mmol/L	HDL-C < 1.03 mmol/L or non-HDL-C ≥ 3.76 mmol/L	FPG ≥ 5.6 mmol/L or 2-h plasma glucose levels from the OGTT ≥ 7.8 mmol/L
IDEFICS (9)	Three or more factors	WC ≥ 90th percentile (age and sex specific)	SBP/DBP ≥ 90th percentile (age, sex and height specific)	TG ≥ 90th percentile (age and sex specific)	HDL-C ≤ 10th percentile (age and sex specific)	HOMA-IR ≥ 90^{t}h percentile or FPG ≥ 90th percentile (age and sex specific)
Cruz et al (10)	Three or more factors	WC ≥ 90th percentile (age and sex specific)	SBP/DBP ≥ 90th percentile (age, sex and height specific)	TG ≥ 90th percentile (age and sex specific)	HDL-C ≤ 10th percentile (age and sex specific)	Impaired glucose tolerance (ADA criterion)
De Ferranti et al (11)	Three or more factors	WC ≥ 75th percentile (age and sex specific)	SBP/DBP≥90th percentile (age, sex and height specific)	TG ≥ 1.1 mmol/L	HDL-C < 1.3 mmol/L	FPG ≥ 6.1 mmol/L
Viner et al (12)	Three or more factors	BMI ≥ 95th percentile (age and sex specific)	SBP/DBP ≥ 95th percentile (age and sex specific)	TG ≥ 1.75 mmol/L or HDL-C <0.9 mmol/L or total cholesterol ≥ 95th percentile		FPG ≥ 5.6 mmol/L or 2-h plasma glucose levels from the OGTT ≥ 7.8 mmol/L or hyperinsulinism
Weiss et al (13)	Three or more factors	BMI ≥ 97th percentile (age and sex specific)	SBP/DBP ≥ 95th percentile (age and sex specific)	TG ≥ 95th percentile (age and sex specific)	HDL-C < 5th percentile (age and sex specific)	Impaired glucose tolerance (ADA criterion)

WC: waist circumference; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; HLD-C: High-density lipoprotein-cholesterol; FPG: fasting plasma glucose; HOMA–IR : homeostasis model assessment – insulin resistance.

Table II. Characteristic of MHO patients.

Only children with all the following criteria fulfilled are classified as MHO	
BMI-SDS	> +2 SD (using the WHO growth charts)
HDL	> 40 mg/dl (> 1.03 mmol/l)
Triglycerides	≤ 150 mg/dl (≤ 1.7 mmol/l)
Blood pressure (systolic and diastolic)	≤ 90th percentile
A measure of glycemia	Fasting plasma glucose ≤ 100 mg/dl (≤ 5.6 mmol/l) (the most commonly used euglycemia criterion)

MHO, metabolically healthy obesity; BMI-SDS, body mass index standard deviation score; HDL, high density lipoprotein.

Anthropometric Measurements

Standing height was measured with a HOLTAIN Limited stadiometer (London, UK) to the nearest 0.1 cm. Weight (to the nearest 0.1 kg) and body composition (trunk and total fat and lean mass) were measured with a TANITA BC-418 MA bioimpedance analyzer (Amsterdam, The Netherlands). BMI was calculated using the formula BMI=kg/m^2. BMI for age was expressed as BMI-SDS based on age- and gender-specific percentiles using the 2006 Italian growth charts[33]. The waist circumference percentile was calculated according to IDEFICS in children and adolescents for the European population[34]. The waist-to-height ratio was also calculated[35]. Blood pressure was measured in sitting position using a mercury sphygmomanometer after a 10 min rest. Measurements were taken from the upper arm with an appropriately sized cuff. SBP and DBP were read to the nearest 2 mmHg and recorded at the appearance and disappearance of Korotkoff's sounds, respectively. The mean value of the last 2 consecutive reading was recorded.

Blood Samples

With the written informed consent of the parents, blood was drawn from the cubital vein of each participant (in sitting position between 8.00 and 10.00 a.m.) after 12 h fasting to determine: fasting plasma glucose (FPG) and insulin (FPI), serum triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), 25-hydroxyvitamin D, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (ɣGT).

Plasma glucose, insulin, triglycerides, HDL-C, AST, ALT, and ɣGT, were analyzed with an ARCHITECT apparatus (Green Oaks, IL, USA).

Glucose and insulin levels were used to estimate basal insulin resistance (IR) by the homeostatic model assessment (HOMA-IR): fasting blood glucose (mg/dl) × fasting insulin (mg/dl)/405[36].

CIMT was measured with color Doppler ultrasound by a vascular surgeon (F.C.) using a ESAOTE Technos MPX Diagnostic Ultrasound Machine (Genova, Italy). Patients lay supine with the head slightly tilted contralateral to the side being examined; shoulder elevation allowed stretching the neck of subjects with a short neck. The far wall of the left and right common carotid artery was scanned 1 cm before the carotid bulb over a length of 1 cm[37]. cIMT was measured by the semiautomatic instrument, which averaged 6 values from each artery and provided the result in micrometers.

Data Processing and Statistical Analysis

The mean cIMT values of MUO, MHO, MetS and control subjects were compared by ANOVA. Data entry and analysis were performed using the Statgraphics-Centurion Ver XV statistical package. Results are presented as mean±standard deviation (SD). Differences in the means of the variables were tested by ANOVA. Data distribution was tested for normality using the Shapiro-Wilk test. A post-hoc Fisher LSD analysis was performed using the independent "*t*" test in case of normally distributed continuous variables. Probability bilateral values (*p*-values) <0.05 were considered statistically significant. With 325 subjects, the study had a power of 90% to detect a moderate effect size (Cohen's *f*:0.25) with 3 df and an α of 0.05 on the CIMT among groups. Given the difference in the number of subjects among groups, the post-hoc analysis of power was based on the average group size. The power analysis was performed by G*POWER Version 3-1-9-2.

Table III. Mean values and SD of the anthropometric and metabolic parameters determined in control, MHO, MUO, and MetS children.

	Controls	MHO	MUO	MetS	
Age	11.47 ± 3.63	12.2 ± 28	11,96 ± 3.3	11.38 ± 2.17	
Weight (kg)	39.21 ± 4.32*	67.2 ± 18.4**	68,1 ± 19.9**	68,3 ± 18.0**	*vs. **$p < 0.05$
Height (cm)	142.4 ± 9.34*	153.1 ± 15.4**	152.3 ± 19.9**	150,3 ± 11.6**	*vs. **$p < 0.05$
BMI	17.8 ± 2.56*	26.2 ± 3.31**	27,5 ± 3.15***	29.7 ± 5,74****	**vs. ****$p < 0.05$ *vs. **,***,****$p < 0.05$
BMI-SDS	0.43 ± 0.11*	1.65 ± 0.73**	2.06 ± 0.59***	2.24 ± 0.57****	**vs. ***$p < 0.05$ **vs. ****$p < 0.05$ *vs. **,***,****$p < 0.05$
Triglycerides (percentile)	43.4 ± 21.6*	53.3 ± 15.1**	53.3 ± 12.3***	65.6 ± 20.1****	**vs. ****$p < 0.05$ ***vs. ****$p < 0.05$ *vs. **,***,****$p < 0.05$
HDL-C (percentile)	59.3 ± 6.21*	35.1 ± 18.4**	19.1 ± 7.2***	4.87 ± 1.87****	**vs. ***$p < 0.05$ **vs. ****$p < 0.05$ ***vs. ****$p < 0.05$ *vs. **,***,****$p < 0.05$
LDL-C (percentile)	5.3 ± 19.5*	63.4 ± 21.6**	65.3 ± 19.3***	70.3 ± 14.5****	*vs. **,***,****$p < 0.05$
SBP (percentile)	72.1 ± 5.2*	81.2 ± 4.2**	90.9 ± 10.1***	99,0 ± 1,2****	**vs.***$p < 0.05$ ***vs. ****$p < 0.05$ *vs. ****$p < 0.05$ *vs. **,***,****$p < 0.05$
DBP (percentile)	65.54 ± 3.56*	80.3 ± 3.0**	82.9 ± 6,2***	96.9 ± 1.91****	**vs. ***$p < 0.05$ ***vs. ****$p < 0.05$ *vs. ****$p < 0.05$ *vs. *,**,***,****$p < 0.05$
HOMA -IR	1.13 ± 0.25	1.75 ± 0.85	1.94 ± 0.41	2.68 ± 1.1	

MHO: metabolically health obese; MUO: metabolically unhealthy obese; Mets: Metabolic Syndrome; BMI: body mass index; HLD-C:High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; HOMA –IR : homeostasis model assessment – insulin resistance.

Results

Based on the IDEFICS criteria, 32 subjects were affected by MetS (14,3 %), 66 were considered MUO (29,4%) and 126 MHO (56,3%).

The mean values and SD of the anthropometric and metabolic parameters determined in MHO, MUO, MetS and control children are summarized in Table III.

The mean cIMT values in MHO, MUO, MetS and control subjects are reported in Table IV for the left cIMT and in Table V for the right cIMT.

Comparison of mean cIMT highlighted a statistically significant difference ($p < 0.05$) between the groups of obese children (MHO, MUO and MetS) and controls for both the left carotid artery (Figure 1) and the right carotid artery (Figure 2).

Discussion

No consensus exists regarding the definition of MetS in children and adolescents[38]. Furthermore, studies published so far have used their own set of variables, number of criteria (three or four) and different cut-off points to define risk factors associated with MetS.

Table IV. Mean left cIMT values in control subjects and MHO, MUO and MetS patients.

Controls	MHO	MUO	MetS
402,87 ± 53,4 *	495 ± 77**	487 ± 73.2***	484,23 ± 86.7****

MHO: metabolically health obese; MUO: metabolically unhealthy obese; Mets: Metabolic Syndrome. *vs. **,***,****$p < 0.05$. **vs. ***,****p = n.s. ***vs. ****p = n.s.

Table V. Mean right cIMT values in control subjects and MHO, MUO and MetS patients.

Controls	MHO	MUO	MetS
377,84 ± 51,93 *	455,13 ± 74,79**	453,65 ± 64,9***	484,36 ± 73,6****

MHO: metabolically health obese; MUO: metabolically unhealthy obese; Mets: Metabolic Syndrome. *vs*. **,***,****$p < 0.05$. **vs*. ***,****p = n.s. ***vs*. ****p = n.s.

The IDEFICS definition of MetS uses sex-specific and age-specific cut-offs based on the distribution of all MetS components in healthy children. For these reasons it gives more balanced weights to the different components of MetS and stresses the importance of adiposity as a risk factor for cardiometabolic disorders later in life[9].

Based on the IDEFICS criteria 32 subjects were affected by MetS (14,3 %), 66 were considered MUO (29,4%) and 126 MHO (56,3%). The incidence of MetS in our casuistry is higher than in previous report[14]; this can be explained by the fact that other definitions tend to classify children based on only three of the four components of MetS. Instead, in the IDEFICS classification each factor – except for adiposity – has equal chances to contribute to the prevalence of the MetS.

Abd El-Hafez et al's study[39] on adult population have already documented an increase in cIMT in the subjects defined as MHO regardless of the metabolic asset.

In addition, many studies[40,41,24] have reported an association between cIMT, atherosclerosis and subsequently myocardial infarction and stroke in adults.

Similar results regarding cIMT and cardiovascular risk have been reported also in pediatric population[42,43]. Moreover, Koskinen et al[44] have shown that isolated obesity represents a cardiovascular risk factor. These results in youth have highlighted the need to act precociously on overweight and obesity.

Our study is the first that applies the IDEFICS classification to a wide range of serious obese patients and evaluates cIMT alterations in subjects with MHO, MUO and MetS.

We did not find significative difference in the value of cIMT in MHO, MUO and MetS subjects, and all groups showed a cIMT statistically higher compared to cIMT of the normal weight subjects.

These results confirm our previous study[27], which showed increased cIMT values in obese MHO and MUO youths compared to non-obese controls and, consequently, a higher CVD risk. These results are partially in contrast with some of the previous studies on the same topic[45].

This discordance can be partly explained by the different criteria of enrollment and definition of MHO, and by the different methods used to measure cIMT. In our study CIMT was measured according to most recent guidelines[37].

It can be assumed that the age of obesity onset is another factor likely implicated in the discrepancy between our data and those of previous studies; our casuistry is composed by subjects

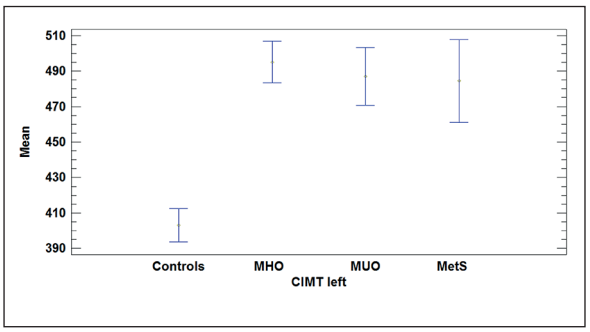

Figure 1. Mean left cIMT in control subjects and MUO, MHO and MetS patients. CIMT: carotid-intima media thickness; MHO: metabolically health obese; MUO: metabolically unhealthy obese; Mets: Metabolic Syndrome.

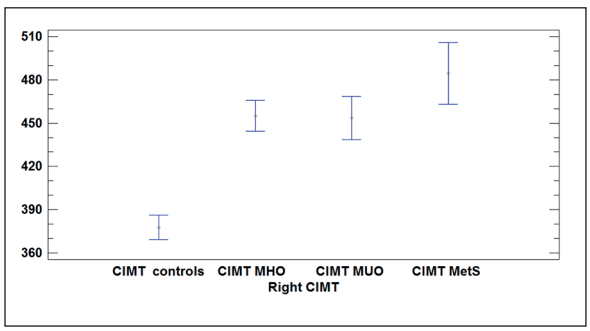

Figure 2. Mean right cIMT in control subjects and MUO, MHO and MetS patients. CIMT: carotid-intima media thickness; MHO: metabolically health obese; MUO: metabolically unhealthy obese; Mets: Metabolic Syndrome.

with early obesity onset and whose obesity has persisted for at least 10 years (data not shown). As shown by Zamrazilova et al[46] in a previous pilot study among obese adolescents, an earlier onset and a longer duration of obesity state could play a leading role in CVD risk's increase.

The strength of our study is to have shown an increase in cIMT regardless the presence of metabolic alterations in the obese child, confirming the existence of a subset of obese children who do not show alterations of metabolic profile. Although this condition appears to be associated with a lower risk of developing Mets, on the other hand, it does not seem to be associated with a lower CVD risk, due to the increase in cIMT compared to healthy controls.

Limitations

Our study has some limitations. The impossibility to differentiate the age of the onset of the obesity state.

Previous studies[47] have highlighted the importance of examining the impact of metabolic pathway-related gene expression that may be implicated in insulin resistance and the mechanisms of development of a metabolically unhealthy obesity profile. In the present work no genetic studies was conducted on patients for this purpose.

Hence, further extensive studies are warranted to validate our preliminary data and draw firm conclusions.

Conclusions

Summarily, our study highlights that MHO, MUO and MetS subjects present an increased cIMT value and that, consequently, these patients need close cardiovascular monitoring, including color Doppler ultrasound examination performed according to the latest Association for European Paediatric Cardiology (AEPC) guidelines, besides dietary and behavioral program, to correct the weight excess and promote the stable achievement of normal weight over time.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval and Consent to Participate

The present study received the consent of the Ethics Committee of the Pediatric Clinic of the University of L'Aquila..

Consent to Publish

All parents signed informed consent for the use of laboratory and anthropometrics data of the subjects studied.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

G.F. and A.V. have conceived and designed the study and revised the manuscript; G.I. and E.A. have acquired and processed data; M.L. and C.G. have analyzed the data and wrote the drafts of the work F.C. performed the echo-color Doppler evaluation. All the Authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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