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Arterial Stiffness and Endothelial Function in Obese Children and Adolescents and Its Relationship with Cardiovascular Risk Factors

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Key Words
Obesity · Children · Endothelial function · Cardiovascular risk factors

Abstract
Background: Obesity is related to an increase in the rates of cardiovascular disease. ***Objective:*** To establish the impact of obesity on vascular function (endothelial function and arterial stiffness) in children and adolescents and its relationship to cardiovascular risk factors. ***Methods:*** In obese (OB) children and adolescents, endothelial function and arterial stiffness were evaluated by a pulse plethysmography method (reactive hyperemia and index of digital volume waveforms, respectively). Data were compared with the non-obese (non-OB) group (body mass index >10th to <97th percentile). Anthropometric parameters, body fat percentage, fasting glucose, lipid profile, insulinemia, HOMA-IR and hemodynamic parameters were determined in both groups. ***Results:*** Body mass index, weight, waist circumference, body fat, insulinemia and HOMA-IR were significantly higher in the OB group. The OB group showed impaired endothelial function (15.8 ± 0.2%, n = 37) compared to the non-OB group (41.4 ± 5%, n = 20; $p < 0.001$) and increased arterial stiffness. Endothelial function was only negatively correlated with waist circumference and HOMA-IR in the OB group, whereas a positive correlation was found between insulinemia and HOMA-IR. ***Conclusions:*** This study shows that impaired vascular function is already present in OB children and adolescents. The fact that obesity is associated with some markers of cardiovascular risk suggests the importance of early lifestyle interventions in this population to prevent cardiovascular disease.

Introduction

The prevalence of obesity in children has increased substantially over the last few years, constituting a global nutritional problem [1]. Obesity in childhood is likely related to an increase in the rates of several diseases such as hypertension, dyslipidemia and diabetes, which are known cardiovascular risk factors [2]. It is well known that the endothelium modulates the response of vascular smooth muscle to hormones, neuromediators and platelet aggregation by releasing relaxing and/or contracting factors. The available evidence indicates that changes in endothelial function are implicated in vascular damage and could initiate the disturbances observed in cardiovascular disorders. The preclinical stage of vascular damage

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begins in childhood and progresses slowly until the development of ischemic complications and organ target damage in adulthood [3–7]. In this sense, impaired endothelial function has been reported in severely obese children (Z-score >3) [8] and obese adults [9]. On the other hand, appropriate vascular function is associated with the degree of vascular compliance. Increased arterial stiffness is associated with an increased risk of cardiovascular events [10].

In recent years, several non-invasive techniques have been developed to assess vascular function in humans. Endothelial function can be evaluated by flow-mediated dilatation following ischemic stimuli (hyperemic response). The assessment of vascular endothelial function using plethysmography to evaluate hyperemic response based on changes in digital arterial pulse-wave amplitude has already been applied in other studies [11, 12] as well as in our laboratory [13]. The digital volume waveform could be effective to evaluate not only endothelial function, but also arterial stiffness. Arterial stiffness is correlated with the aortic augmentation index [14] which indicates alterations on vascular-ventricular coupling and could be associated with cardiovascular mortality [15]. Moreover, arterial stiffness is used as an independent prognostic indicator for cardiovascular disease [16].

Although the body mass index (BMI) is used to diagnose obesity in both children and adults, BMI is not able to determine body fat distribution. On the other hand, it has been shown that the metabolic and cardiovascular risk related to obesity is associated with the percentage of visceral fat, which is manifested clinically as central or abdominal obesity. In adults, it is known that the waist circumference reflects the amount of abdominal fat with higher sensitivity and specificity than other anthropometric indicators. Similarly, it has been showed that in prepubertal and pubertal children, the waist circumference is a good predictor of metabolic and cardiovascular diseases in adulthood [17]. On the other hand, there is an increasing amount of data showing that being overweight and obesity during childhood and adolescence is associated with hyperinsulinemia and insulin resistance which are indicators of cardiovascular risk [2].

Based on these considerations, we hypothesized that vascular dysfunction is present early in obese children and adolescents, and this could be associated with cardiovascular risk indicators. To test this hypothesis, the objective of the present work was to study the vascular function (endothelial function and arterial stiffness) based on non-invasive assessments in children and adolescents and to correlate vascular function with cardiovascular risk factors.

Material and Methods

Obese (OB) male children and adolescents (Z-score ≥2 and BMI ≥97th percentile [18]) presenting to the endocrinology outpatient service of the Hospital del Niño Jesús (Tucumán, Argentina) were recruited consecutively.

The following exclusion criteria were used: the presence of diabetes, hypertension, cardiovascular disease or other pathologies; regular medications or a clinical evidence of infections at the moment of inclusion. A non-obese (non-OB) control group (Z-score <2 and BMI >10th and <97th percentile [18]) of similar age (range 7–16 years in both groups) was recruited among the friends or relatives of the OB boys who attend the Nicolas Avellaneda School (Aguilares-Tucumán, Argentina). For the present study, 37 OB and 20 non-OB children were included.

According to institutional guidelines, the informed consent form was signed by all participants and their parents for both the assessment of vascular function and for obtaining blood samples.

The anthropometric parameters: body weight, height, BMI and waist circumference were measured and the percentiles were calculated according to the guidelines of the Argentinean Paediatric Society [18]. Body fat percentage (based on bioelectrical impedance; Omron HBF-306C Body Fat Analyzer) and arterial blood pressure [19] were also measured. Laboratory tests including fasting glucose, lipid profile, blood count, insulin levels and HOMA-IR were performed.

Endothelial Function Assessment

Endothelial function was evaluated using a non-invasive digital volume waveform plethysmography technique that was previously used by our laboratory [13]. The changes in the amplitude of the digital pulse wave were recorded with an electrocardiograph using an adapter designed by our laboratory. The hyperemic response was produced by flow-mediated vasodilatation. Before the start of the recording phase, the patient was asked to hold their breath for 10 s (pre-occlusion phase). Then, and in order to obtain complete arterial occlusion, the sphygmomanometer cuff was insufflated to 50 mm Hg above systolic arterial pressure by 5 min (occlusion phase). The sphygmomanometer cuff was then deflated, and after 2 min another 10 s, apnea was required to obtain the post-occlusion recording (post-occlusion phase). The register obtained from each subject was scanned to measure the amplitude of the pulse wave using the ImageJ 1.43u Software (Bethesda, Md., USA). Ten waves were averaged in each subject from each phase to compare the pre- vs. post-occlusion phases (Δ).

Arterial Stiffness Assessment

Arterial stiffness was evaluated using the plethysmography system. The procedures were similar to those described above. Blood pressure was measured and a graphical record of 10 pulse waves was obtained. To rule out the waves produced by ectopic beats, a simultaneous electrocardiogram was performed. The register obtained from each subject was scanned to determine the stiffness index, which was calculated using the following formula: Maximal systolic peak (100)/Maximal diastolic peak. In each subject, 10 pulse waves were averaged. In 3 OB patients the stiffness index could not be calculated because their records did not present a dichotic notch in the pulse-wave record, but rather a sine wave.

Statistical Analysis

Data were expressed as the mean ± SE. Results were considered to be significant when $p < 0.05$. GraphPad Prism 4.0 and the Statistica 5.0 statistical software package were used. Student's t test for paired and grouped ANOVA or the Pearson correlation coefficient was also used.

Results

The clinical characteristics of the patients are shown in table 1. BMI and body weight were higher in the OB group than in the non-OB group. Similarly, waist circumference was not only higher in OB patients than in non-OB patients, but was also higher than the 90th percentile, indicating that this parameter was altered [20]. No differences between OB and non-OB were observed in age, height, birth weight and arterial blood pressure. On the other hand, body fat percentage, measured using an impedancimetric method, was higher in the OB group (32.1 ± 1%, n = 35) than in the non-OB group (17.1 ± 1%, n = 20; $p < 0.001$). Although a positive correlation between BMI and waist circumference was observed in both groups – non-OB (Pearson r = 0.6403, 95% CI 0.2759–0.8438, n = 20; $p < 0.01$) and OB (Pearson r = 0.3345, 95% CI 0.01166–0.5942, n = 37; $p < 0.05$) – waist circumference was only positively correlated with body fat percentage in the OB group (Pearson r = 0.4592, 95% CI 0.1486–0.6873, n = 35; $p < 0.05$; non-OB: Pearson r = 0.4334, 95% CI –0.01139 to 0.7350, n = 20; p = NS).

In relation to lipid profile, normal values in both groups were observed. No differences between the OB and non-OB group were observed in values of total cholesterol (non-OB 150.3 ± 5 mg/dl, n = 10 vs. OB 163.4 ± 7, n = 17; p = NS), LDL cholesterol (non-OB 94.9 ± 4 mg/dl, n = 10 vs. OB 101.1 ± 6, n = 17; p = NS), HDL cholesterol (non-OB 44.5 ± 2 mg/dl, n = 10 vs. OB 40.4 ± 2, n = 17; p = NS) and triglycerides (non-OB 87.0 ± 9 mg/dl, n = 10 vs. OB 97.3 ± 8, n = 17; p = NS).

In relation to fasting glycemia, although normal values in both groups were observed, the OB patients showed significantly higher levels (non-OB 77.0 ± 2 mg/dl, n = 12 vs. OB 87.9 ± 2, n = 19; $p < 0.001$). On the other hand, both insulinemia and HOMA-IR were elevated in OB patients (fig. 1). Interestingly, glycemia values were only positively correlated in the OB group with insulinemia (Pearson r = 0.5750, 95% CI 0.1633–0.8161, n = 19; $p < 0.05$) and HOMA-IR (Pearson r = 0.5930, 95% CI 0.1899–0.8251, n = 19; $p < 0.01$). Furthermore, insulinemia was only positively correlated in the OB group with HOMA-IR (Pearson r = 0.8860, 95% CI 0.7224–0.9556, n = 19; $p < 0.001$).

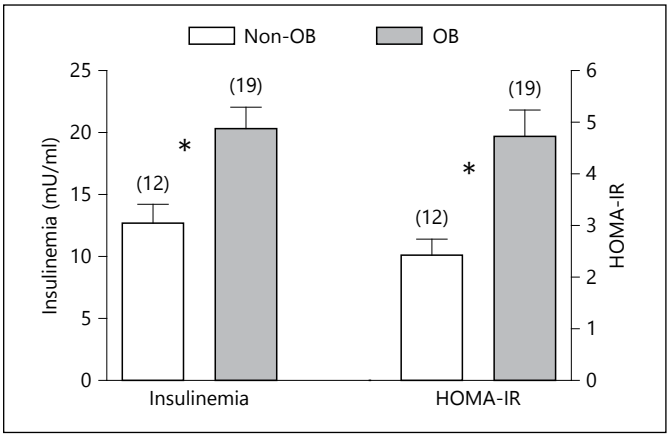

Fig. 1. Values of insulinemia and HOMA-IR in non-OB and OB patients. * $p < 0.01$ OB vs. non-OB; unpaired Student's t test. Data are expressed as mean ± SE. The number of subjects is in parentheses.

Table 1. Clinical characteristic of the children and adolescents studied

	Non-OB (n = 20)	OB (n = 37)
Age, years	13.6±0.5	13.1±0.4
BMI, percentile	77.2±3.8	99.9±0.2***
Body weight, percentile	60.0±5	93.8±2***
Height, percentile	51.5±7	60.3±5
Birth weight, kg	3.6±0.4	3.5±0.1
Waist circumference, percentile	65.0±5	98.7±1***
Blood pressure, mm Hg		
Systolic	103.3±3	107.1±2
Diastolic	64.5±2	64.8±2
Heart rate, bpm	83.6±3	80.5±2

Data are expressed as mean ± SE. *** $p < 0.001$ non-OB vs. OB; Student's t test. The number of subjects is in parentheses.

In relation to endothelial function, the hyperemic response was significantly higher in the non-OB group than in the OB group (fig. 2). These values correspond to 41.4 ± 5 and 15.8 ± 0.2% of increased post-occlusion records in the non-OB group and OB group, respectively ($p < 0.001$). On the other hand, only hyperemic response was negatively correlated in the OB group with waist circumference (fig. 3a) and HOMA-IR (fig. 3b).

Arterial stiffness was higher in the OB group than the non-OB group (65.4 ± 2%, n = 34 vs. 53.1 ± 3%, n = 20, respectively; $p < 0.001$). No correlations between arterial stiffness with waist circumference and arterial stiffness

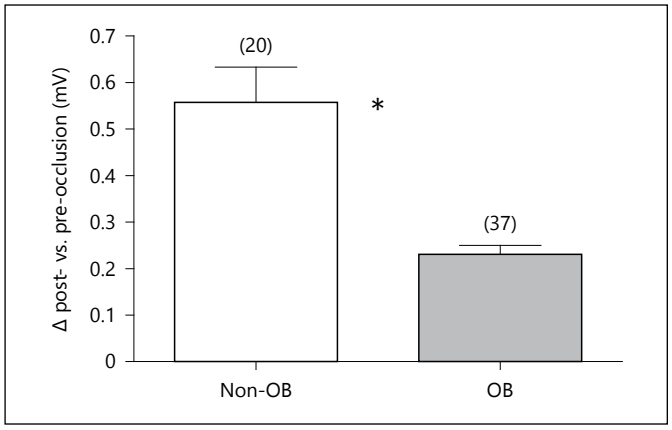

Fig. 2. Hyperemic response in non-OB and OB patients expressed as millivolts. * $p < 0.001$ OB vs. non-OB; unpaired Student's t test. Data are expressed as mean ± SE. The number of subjects is in parentheses.

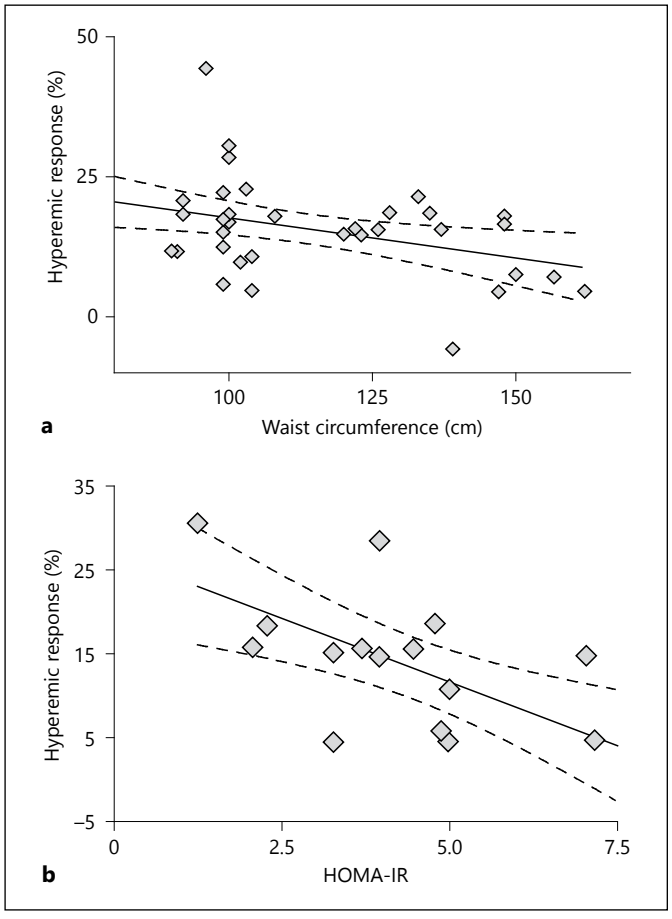

Fig. 3. Correlation between hyperemic response and (**a**) waist circumference in OB patients (Pearson r = –0.4016, 95% CI –0.6421 to –0.0089, n = 37; $p < 0.05$) and (**b**) HOMA-IR in OB patients (Pearson r = –0.5082, 95% CI –0.7820 to –0.07012, n = 19; $p < 0.05$).

with HOMA-IR were detected between the OB and non-OB group (Pearson r = 0.01366, 95% CI –0.3261 to 0.3503, n = 35; p = NS, and Pearson r = –0.1179, 95% CI –0.5665 to 0.3847, n = 19; p = NS, respectively).

Discussion

The principal finding of this study was that decreased endothelial function and increased arterial stiffness were present in OB children and adolescents. Although this study included children with normal lipid profiles, glycemia and blood pressure, it is necessary to note that the OB group presented an increased waist circumference and a positive correlation between waist circumference and body fat percentage. In agreement with our findings, previous reports indicate that the assessment of waist circumference in children may be the best indicator to identify future risk for obesity-related complications [21]. Our population did not present the classic cardiovascular risk factors, but our results suggest an obesity-related cardiovascular risk in childhood. Moreover, the OB group presented basal insulinemia and altered HOMA-IR. On the other hand, interestingly, although fasting glycemia was within normal limits, the OB group showed significantly higher basal values than the non-OB group. In addition, glycemia values were positively correlated with insulinemia and HOMA-IR. In agreement with our findings, Weiss et al. [22] showed that obesity in children and adolescents is associated with insulin resistance and alterations of glycemic homeostasis. The importance of determining the HOMA-IR to diagnose pathological states related to cardiovascular risk, such as metabolic syndrome, has been highlighted recently by other authors [23]. Consistent with this trend, it has been postulated that alterations in HOMA-IR in childhood could predict development of cardiovascular diseases in adulthood [24]. Furthermore, some studies showed that overweight in adolescence increased the risk of morbidity and mortality from cardiovascular diseases in adulthood, independent of adult weight [25].

In the present study we evaluated endothelial function determined by hyperemic response. The OB group presented impaired endothelial function evidenced by a decreased flow-mediated vasodilation after the hyperemic maneuver. This topic has been extensively studied in adult patients but not in children. There are few non-invasive studies of vascular function in children and adolescents with obesity without diabetes or another associated pathology. Consistent with our findings, Tounian et

al. [8] demonstrated endothelial dysfunction in children. However, their study was performed in severely OB children (Z-score >3), unlike our population (Z-score >2). The fact that endothelial function correlates negatively with HOMA-IR indicates that the early vascular abnormalities in OB patients may be involved in alterations of glycemic homeostasis. In this sense, Suys et al. [26] showed that adolescents with diabetes presented impaired endothelial function. On the other hand, and consistent with our findings, Caballero et al. [27] reported that vascular alterations could precede overt diabetes. Another finding that supports this view is the fact that in our study, endothelial function is negatively correlated with waist circumference.

In our study, the OB group showed elevated arterial stiffness assessed by the index of diastolic/systolic features of the pulse wave. It is known that arterial stiffness is an independent predictor of cardiovascular events in adulthood [16]. Moreover, it has been proposed that 'destiffening' could be a strategy for the prevention of hypertension and cardiovascular diseases [28, 29]. Alterations of arterial stiffness were observed in young patients with cardiovascular risk factors such as smoking [30]. Consistent with our study, Zebekakis et al. [31] showed increased arterial stiffness in OB adolescents and other authors proposed that lower arterial elasticity may lead to hypertension in the future [32]. Moreover, Koivistoinen et al. [33] indicated that children with metabolic syndrome presented arterial stiffness in adulthood.

In conclusion, OB children and adolescents have impaired endothelial function and increased arterial stiffness. The fact that these alterations were correlated with the presence of an increased waist circumference, insulinemia and HOMA-IR, even in the absence of classic cardiovascular risk factors or associated pathology, indicates that obesity is implicated in cardiovascular risk. Finally, the fact that this study was performed in children and adolescents highlights the importance of early lifestyle changes in this population to prevent the occurrence of cardiovascular disease.

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