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Homocysteine and Cardiovascular Risk Factors in Overweight or Obese Children and Adolescents

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Abstract

Introduction: Among the extrinsic factors, homocysteine (Hy) stands out, which is an intermediate amino acid of the intracellular metabolism of methionine involved in the process of cellular oxidation, which promotes the installation of atheromatous plaques and, therefore, is considered as an emerging cardiovascular risk factor. Objective: To evaluate the plasma homocysteine levels (Hy) in overweight or obese children and adolescents and their relation with cardiovascular risk factors. Methods: A cross-sectional study was conducted from July 2011 to May 2012 with overweight or obesity children and adolescents aged 2 to 18 years followed at the Center for Childhood Obesity (IOC), Campina Grande-PB. A structured form was used to record demographic, socioeconomic and clinics variables and the patients underwent laboratory tests to define their lipid and glucose profiles and measurement of plasma Hy levels. Results: The study evaluated a total of 165 children and adolescents with mean age of 12.5 (±2.5) years; the majority were female (57.0%). Regarding the lipid profile, there was more individuals with low HDL cholesterol (88.5%). Plasma Hy levels were high in 24.2% of the sample. The mean Hy levels ranged from 4.3 to 18.9 µmol/L, being higher in males, obese adolescents and also in patients with high insulin levels and resistance. Conclusions: The results shown in this study emphasize the importance of detecting and controlling the plasma Hy levels as an independent cardiovascular risk factor, and the need for further studies to evaluate the clinical and biological factors related to alterations in its metabolism.

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Keywords

Homocysteine, Cardiovascular Diseases, Child, Adolescent, Obesity

1. Introduction

A significant increase in overweight and obesity among children and adolescents has been observed in developed and developing countries. In this context, overweight is an important risk marker for various diseases, particularly cardiovascular diseases (CVD) [1].

The etiogeny of CVD is associated with some risk factors that can be classified into two groups: intrinsic, or not susceptible to modification (age, sex, heredity) and extrinsic factors, or those that can be modified (dyslipidemia, diet, smoking, physical inactivity) [2].

Among the extrinsic factors, homocysteine (Hy) stands out, which is an intermediate amino acid of the intracellular metabolism of methionine involved in the process of cellular oxidation, which promotes the installation of atheromatous plaques and, therefore, is considered as an emerging cardiovascular risk factor [3].

Plasma Hy levels can be determined by genetic, biological, nutritional, hormonal and lifestyle factors [4]. Therefore, it is essential to investigate possible factors that are directly relate to the Hy concentrations such as enzyme deficit, low consumption of folate and vitamin B12, age, being male, high alcohol consumption and estradiol levels [5].

Considering, therefore, that the atherosclerotic process begins long before clinical aspects are detected, the cardiovascular risk factors, traditional or not, arise mainly with excess weight and the fatty streaks are observed even in childhood, is appropriate deepen the knowledge about childhood obesity and cardiovascular disease through research of its risk factors, such as Hy, especially since this intermediate of protein metabolism is involved in the understanding of vascular obstruction caused by atherosclerotic plaques, and therefore, necessary studies to identify factors associated with hyperhomocysteinemia [6].

Given the above, the aim of this study was to evaluate plasma Hy levels in overweight or obese children and adolescents and their relationship with cardiovascular risk factors.

2. Methodology

A cross-sectional study with quantitative approach was conducted, with data being collected from July 2011 to May 2012 with patients followed at the Center for Childhood Obesity (IOC), located at the "Elpídeo de Almeida" Institute of Health in Campina Grande-PB. A cross-sectional studies are viewing the status of a population in a given moment, as snapshots of reality. Describe the situation in a given time and for this reason often are classified wrongly as descriptive, as in reality, these studies allow the first time analysis of an association. The quantitative analysis of the studies, in turn, refers to submission of survey data numerically, classified and analyzed using statistical techniques.

This study is part of a broader project entitled "*Cardiovascular and type*-2 *diabetes risk in obese children and adolescents with metabolic syndrome*: *a longitudinal study*", approved by the Ethics Committee of the State University of Paraíba, under CAAE No. 0256.0.133.000-11.

The convenience sample was composed of overweight/obese children and adolescents aged from 2 and 18 years. In this period, 200 children and adolescents were followed at the IOC, of whom 26 did not accept performing blood collection; five were excluded as they were older than 19 years and four for having normal nutritional status, totaling 165 individuals.

Nutritional status was determined by calculating the body mass index (BMI). Patients with from 85^{th} to 95^{th} percentiles were classified as overweight and as obese those with $\geq 95^{th}$ percentile, defined as recommended by the Centers for Disease Control and Prevention [7]. Children, adolescents and their mothers were weighed on calibrated scales with accuracy of 0.1 kg. Height was measured in rigid stadiometer with accuracy of 0.01 cm. To assess maternal nutritional status, the criteria proposed by the World Health Organization—WHO were used [8].

Regarding family history of CVD (Systemic hypertension, type-2 diabetes, hypercholesterolemia, hypertriglyceridemia, acute myocardial infarction and stroke), the study considered the report of at least one of these events in first-degree relatives: parents, grandparents, aunts and uncles.

Waist circumference was measured at the midpoint between the lateral iliac crest and the lower edge of the last rib during expiration. Values above the 90th percentile for age and sex were considered high, according to criteria proposed by the International Diabetes Federation [9], observing the upper limit of 88 cm for girls and 102 cm for boys, according to the National Cholesterol Education Program/Adult Treatment Panel III.

Blood pressure was measured three times by auscultation, with interval of 2 minutes, considering the average of the last two measures. The criteria for the diagnosis of high blood pressure followed the VI Brazilian Guidelines on Hypertension [10]. For individuals up to 17 years of age, those with systolic and/or diastolic blood pressure greater than or equal to the 90th percentile have been diagnosed with high blood pressure. For individuals older than 17 years, those with systolic blood pressure greater than or equal to 140 mmHg and diastolic blood pressure greater than or equal to 90 mmHg have been diagnosed with high blood pressure.

For biochemical analyzes, patients were submitted to a 12-hour fasting period before blood collection of 10 mL. Triglycerides, total cholesterol and fractions and glucose levels were measured by the enzymatic colorimetric method. The cutoff points for unsatisfactory lipid levels were determined by the I Guideline for Prevention of Atherosclerosis in Childhood and Adolescence [11]. Hyperglycemia was determined from values equal to or greater than 100 mg/dL, in accordance with criteria established by the American Diabetes Association [12]. Regarding insulin, measured by chemiluminescence, values greater than or equal to 15 μUI/mL were considered high (61). The insulin resistance level (HOMA-IR) was calculated as the product of insulin levels by blood glucose and dividing the result by 22.5, with HOMA-IR $\geq$ 2.5 being considered as cutoff [13].

The method used for Hy determination was the High Performance Liquid Chromatography (HPLC) and the reference values adopted for this study were those suggested by Refsum *et al*. [14], which established values higher than or equal to 10 mmol/L as high for individuals under 14 years of age, and values higher than or equal to 15 mmol/L as high for those aged 15 years or more.

Biochemical determinations were performed at the Clinical Laboratory of the State University of Paraíba, except for insulin dosages and Hy, which were performed at another laboratory, with funding by research incentives, certified by the Brazilian Society of Clinical Analyses.

Descriptive statistical analysis was carried out by mean, standard deviation and frequencies, and data were analyzed using the SPSS software, version 17.0. For the association between Hy and the other cardiovascular risk factors, the Chi-square test was used and to compare means, analysis of variance was used. The significance level adopted was 5.

3. Results

Of the total of 165 children and adolescents evaluated, the mean age was 12.5 (±3.5) for the total sample, and 8.9 (±2.1) for the children and 14.3 (±4.1) years for the adolescents. Most were female (57.0%), adolescents (75.2%) and non-white skin color (63.6%). Demographic and socioeconomic variables are described in **Table 1**.

Table 2 describes the variable family history. The majority of patients showed three or more antecedents (78.8%), and the most frequent was hypertension (84.8%).

In relation to the other clinical variables, 83.0% of the sample showed nutritional status of obesity. Regarding the lipid profile, there is a greater number of individuals with low HDL cholesterol (88.5%). Plasma Hy levels were high in 25.0% of the sample.

Table 3 shows the frequency and odds ratios with respective confidence intervals (CI 95%) for cardiovascular risk factors according to the plasma Hy levels.

The mean Hy value was 9.2 μmol/L (±2.9), with minimum value of 4.3 μmol/L and maximum value of 18.9 μmol/L. When compared by cardiovascular risk factor, it was found that the means were significantly higher in the following groups: males, adolescents, patients with obesity, higher insulin levels and presence of insulin resistance (**Table 4**). There was statistical significance between Hy and age, sex, and insulin resistance.

4. Discussion

The fact that CVD may originate in childhood and adolescence leads to the need for a wide investigation of cardiovascular risk factors in this phase, aiming at early intervention and thus reducing morbidity and mortality in adulthood [15].

According to Bereson *et al*. [16], cardiovascular risk is directly proportional to the obesity degree. The IOC

Table 1. Percentage distribution of demographic and socioeconomic data, according to the sex of overweight/obese children and adolescents followed at the IOC (n = 165), Campina Grande, 2011-2012.

Variables	Sex	
	Male	Female
	n (%)	n (%)
Age group		
Child (2 to 9 years)	21 (51.2)	20 (48.8)
Adolescent (10 to 19 incomplete years)	50 (40.3)	74 (59.7)
Nutritional Status of Children/Adolescents		
Overweight (85 ≤ pBMI < 95)	08 (28.6)	20 (71.4)
Obesity (pBMI ≥ 95)	63 (46.0)	74 (54.0)
Skin color		
White	25 (41.7)	35 (58.3)
Non-white	46 (43.8)	59 (56.2)
Type of school		
Private	34 (41.5)	48 (58.5)
Public	36 (44.4)	45 (55.6)
Not enrolled	01 (50.0)	01 (50.0)
Total family income		
≤two MW	38 (46.9)	43 (53.1)
>two MW	33 (39.3)	51 (60.7)
Number of household members		
2 - 5	61 (42.4)	83 (57.6)
6 or more	10 (47.6)	11 (52.4)
Maternal Nutritional Status		
Underweight	00 (0.0)	01 (100.0)
Normal weight	10 (32.3)	21 (67.7)
Overweight	24 (44.4)	30 (55.6)
Obesity	37 (46.8)	42 (53.2)
Maternal schooling		
≤8 years of study	17 (37.0)	29 (63.0)
≥9 years of study	54 (45.4)	65 (54.6)

Table 2. Percentage distribution of family history of overweight/obese children and adolescents followed at the IOC (n = 165), in relation to the presence, number and type of antecedent, Campina Grande, 2011-2012.

Variables	n (%)
Presence of antecedents	
Yes	162 (98.2)
No	03 (1.8)
Number of antecedents	
1 - 2	35 (821.2)
3 or more	130 (78.8)
Type of antecedent	
Systemic Hypertension	140 (84.8)
Obesity	122 (73.9)
Type-2 Diabetes Mellitus	109 (66.1)
Hypercholesterolemia	86 (52.1)
Acute Myocardial Infarction	56 (33.9)
Hypertriglyceridemia	53 (32.1)
Stroke	45 (27.3)

Table 3. Frequency and odds ratios with respective confidence intervals (CI 95%) for cardiovascular risk factors according to the plasma Hy levels of overweight/obese children and adolescents followed at IOC (n = 165), Campina Grande, 2011-2012.

Variables	Total (n = 165)	Hy levels: High Hy (n = 40) n (%)	Hy levels: Normal Hy (n = 125) n (%)	OR (CI 95%)	*p**
Waist circumference					
Increased (>90th percentile)	121 (73.3)	28 (23.1)	93 (76.9)	0.803 (0.366 - 1.763)	0.584
Normal	44 (26.7)	12 (27.3)	32 (72.7)		
Systolic Blood Pressure					
High (≥90th percentile)	24 (14.5)	05 (20.8)	19 (79.2)	0.797 (0.277 - 2.293)	0.448
Normal	141 (85.5)	35 (24.8)	106 (75.2)		
Diastolic Blood Pressure					
High (≥90th percentile)	46 (27.9)	09 (19.6)	37 (80.4)	0.690 (0.299 - 1.592)	0.503
Normal	119 (72.1)	31 (26.1)	88 (73.9)		
Total Cholesterol					
High (≥150 mg/dL)	101 (61.2)	19 (18.8)	82 (81.2)	0.474 (0.230 - 0.977)	0.041
Normal	64 (38.8)	21 (32.8)	43 (67.2)		
LDL Cholesterol					
High (≥100 mg/dL)	83 (50.3)	18 (21.7)	65 (78.3)	0.717 (0.350 - 1.470)	0.363
Normal	79 (49.7)	22 (27.8)	57 (72.2)		
HDL Cholesterol					
Low (<45 mg/dL)	146 (88.5)	38 (95.0)	108 (86.4)	2.991 (0.660 - 13.553)	0.111
Normal	19 (11.5)	02 (5.0)	17 (13.6)		
Triglycerides					
High (≥100 mg/dL)	104 (63.0)	22 (21.2)	82 (78.8)	0.641 (0.311 - 1.322)	0.227
Normal	61 (37.0)	18 (29.5)	43 (70.5)		
Blood glucose					
High (≥100 mg/dL)	03 (1.9)	01 (33.3)	02 (66.7)	1.577 (0.139 - 17.864)	0.568
Normal	162 (98.1)	39 (24.1)	123 (75.9)		
Insulin levels					
High (≥15 µUI/mL)	40 (25.0)	12 (30.0)	28 (70.0)	1.485 (0.670 - 3.292)	0.329
Normal	125 (75.0)	28 (22.4)	97 (77.6)		
Insulin resistance					
Present (HOMA ≥ 2.5)	56 (33.9)	16 (28.6)	40 (71.4)	1.417 (0.679 - 2.957)	0.352
Absent	109 (66.1)	24 (22.0)	85 (78.0)		

*Chi-square test.

Table 4. Mean values, standard deviation and confidence interval of Hy levels according to the other cardiovascular risk factors of overweight/obese children and adolescents followed at the IOC (n = 165), Campina Grande, 2011-2012.

Variables	Homocysteíne (μmol/L)		Variables	Homocysteíne (μmol/L)	
	Mean ± SD (CI 95%)	p^*		Mean ± SD (CI 95%)	p^*
Sex			**Total Cholesterol**		
Male	9.9 ± 3.4 (9.1 - 10.7)	0.005	High	9.0 ± 2.7 (8.5 - 9.5)	0.310
Female	8.7 ± 2.3 (8.2 - 9.1)		Normal	9.5 ± 3.1 (8.7 - 10.2)	
Age			**HDL Cholesterol**		
Children	8.4 ± 1.9 (7.8 - 9.0)	0.036	Low	9.3 ± 3.0 (8.8 - 9.8)	0.096
Adolescents	9.5 ± 3.1 (8.9 - 10.0)		Normal	8.1 ± 1.3 (7.5 - 8.8)	
Nutritional status			**LDL Cholesterol**		
Overweight	9.0 ± 3.1 (7.8 - 10.3)	0.757	High	9.1 ± 2.8 (8.5 - 9.8)	0.649
Obesity	9.2 ± 2.8 (8.7 - 9.7)		Normal	9.3 ± 2.9 (8.8 - 10.0)	
Waist circumference			**Blood glucose levels**		
Increased	9.1 ± 2.7 (8.6 - 9.6)	0.322	High	8.5 ± 1.4 (5.1 - 11.9)	0.671
Normal	9.6 ± 3.2 (8.6 - 10.6)		Normal	9.2 ± 2.9 (8.8 - 9.7)	
Systolic blood pressure			**Insulin levels**		
High	8.5 ± 2.0 (7.6 - 9.3)	0.182	High	10.0 ± 3.2 (8.8 - 10.9)	0.081
Normal	9.3 ± 3.0 (8.8 - 9.8)		Normal	9.0 ± 2.7 (8.5 - 9.4)	
Diastolic blood pressure			**Insulin resistance**		
High	9.0 ± 2.8 (8.1 - 9.8)	0.504	Present	10.0 ± 3.5 (9.1 - 10.9)	0.011
Normal	9.3 ± 2.9 (8.8 - 9.8)		Absent	8.8 ± 2.4 (8.3 - 9.3)	
Triglycerides					
High	9.1 ± 3.1 (8.5 - 9.7)	0.437			
Normal	9.4 ± 2.5 (8.8 - 10.1)				

*Analysis of variance.

sample showed a common characteristic: excess weight. In Brazil, the process of nutritional transition observed in recent decades indicates increased overweight and obesity prevalence in the general population. Leal *et al.* [17] conducted a population-based study with children and adolescents from 5 to 19 years of age and found an overweight prevalence of 13.3% in the state of Pernambuco, 9.5% of overweight and 3.8% of obesity.

In relation to the maternal nutritional status, this study found that 24.1% of mothers were overweight, a fact that corroborates the results found by Silva, Baladan and Motta [18], who studied obese children and adolescents aged 7 - 12 years and their parents and found that the nutritional status of their mothers was significantly changed (29.9% overweight).

In a study by Strufaldi, Silva and Puccini [19], from the 929 schoolchildren assessed, 328 (35.3%) reported positive family history for CVD; of these, 20.0% had a history of early CVD, 17.3% of hypertension, 8.5% of obesity, 5.9% of dyslipidemia, and 3.7% of type-2 DM. In our study, however, there was a higher prevalence (97.7%) of children and adolescents with reported family history, highlighting the occurrence of hypertension (82.2%), and grandparents were the relatives most reported in these antecedents (93.6%). Regarding the family history, there was a prevalence of three or more antecedents (78.8%).

Studies indicate that systemic hypertension can start in childhood. In 2012, Rinaldi *et al.* [20] evaluated 903 children and adolescents from Botucatu (SP) with mean age of 9.3 (±2.5) years and found hypertension prevalence of 2.9%. Freitas *et al*. [21], in turn, assessed a sample of 184 adolescents, of which 9.8% showed high systolic blood pressure and 12.5% increased diastolic blood pressure. With similar frequencies and using the same cutoff points of these studies, 14.5% of the IOC sample showed high systolic blood pressure and 27.9% high diastolic blood pressure, showing a strong relationship between overweight and high blood pressure.

Obesity leads to changes in lipid metabolism. The WHO has reported that approximately 84.0% of adolescents live in developing countries such as Brazil, and that this percentage in relation to the other groups increased, but little importance has been given to the determination of the lipid profile in adolescence [22]. However, recent studies have claimed that hypertriglyceridemia associated with high LDL cholesterol levels increases by six times the risk of CVD, and that the development of atherosclerosis in obese adolescents is enhanced by increased plasma cholesterol levels. In addition, the oxidation of LDL cholesterol particles in the arterial walls is considered the main event for the development of atheromatous plaques [23].

Regarding the lipid profile in 2010, Araki, Barros and Santos [24] evaluated 297 children and adolescents and showed disturbing results in relation to HDL cholesterol levels, since 41.7% of the sample had low levels. In this study, however, using the same cutoff points, there was a greater frequency (88.5%) of HDL cholesterol below the threshold used, which is a worrisome fact, since increased serum levels of this lipoprotein reduce cardiovascular risk due to reverse cholesterol transportation, removing it from the cells and transporting it to the liver for subsequent excretion [25].

In addition to the cardiovascular risk factors discussed above, high plasma Hy levels are an emerging risk factor for CVD (3). The pathogenesis of vascular injury determined by Hhy includes endothelial cell injury, growth of the smooth vascular muscle, increased platelet aggregation, increased LDL cholesterol oxidation with deposition on the vascular wall and direct activation of the coagulation cascade [26]. Thus, the plasma Hy levels may be influenced by biological changes such as sex and age, and other clinical factors such as dyslipidemia [27]. In this sense, the literature shows the relationship between increased synthesis of cholesterol and elevated Hy levels through studies in cultured liver cells, also showing the increased expression of the Hydroxy-Methyl-Glutaryl-Coenzyme A reductase enzyme, responsible for the formation of cholesterol [28] [29].

Regarding sex, Almeida *et al.* [30] showed that the Hy concentrations tended to be higher in men than in women, because women have the protective effect of estrogen. With advancing age, these levels also increase, remaining as a risk factor for coronary heart disease, aggravated by the deficiency of vitamins. The study by Kerr *et al*. [31] with children and adolescents between 4 and 18 years of age found that the Hy concentrations gradually increased with increasing age and were higher in boys (6.3 mmol/L) than in girls (6.2 mmol/L). Similarly, Akanji, Thalib and Al-Isa [32] studied adolescents from 10 to 19 years of age and concluded that there is a direct relationship between increasing age and plasma Hy levels and that boys showed total average Hy levels significantly higher (8.25 μmol/L).

The IOC sample studied has diagnosis of overweight or obesity, which is a characteristic that contributes to the development of atherosclerosis. It is believed that factors related to lifestyle may interfere with elevated plasma Hy levels. Accordingly, the prevalence of overweight can negatively influence the plasma Hy concentrations, considering that obesity is characterized by excessive consumption of high-calorie foods, poor of protein and vitamins [33]. Therefore, the average Hy value was higher in children or adolescents with diagnosis of obesity (9.3 μmol/L). In addition, the work by Brasileiro *et al*. [34], whose sample consisted of adolescents with and without excess weight, showed higher Hy levels in overweight individuals.

Regarding the glucose profile, the mean Hy value was higher in patients with elevated fasting insulin and / or insulin resistance. Studies have shown that elevated plasma insulin levels can lead to Hhe, possibly due to changes in enzymes involved in the Hy metabolism, especially cystathionine-β-synthase, involved in the transsulfuration pathway [35] [36].

Finally, is important to consider some limitations. The data presented are from a cross-sectional design, which does not require the composition of a control group for comparison, so it was not possible to assess the temporal sequence between exposure of interest on the biochemical factors studied. yet, because they are information provided from a convenience sample, the study did not allow the extrapolation of results and needed to conduct population surveys of this problem.

5. Conclusion

The mean plasma Hy concentrations are higher in males, adolescents and patients with insulin resistance, which is important when one considers that biological and clinical characteristics reduce the metabolism of this intermediate amino acid and that all these factors are associated with cardiovascular risk. Thus, these results can guide public health actions aimed to reduce, since childhood, the risk of developing CVD and expenses related to their treatment.

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