ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 10, Issue, 10, pp. 41306-41311, October, 2020
https://doi.org/10.37118/ijdr.20188.10.2020

RESEARCH ARTICLE OPEN ACCESS

PERSISTENT METABOLIC SYNDROME AND NEW CARDIOVASCULAR RISK MARKERS IN OVERWEIGHT OR OBESE CHILDREN AND ADOLESCENTS

Anajás da Silva Cardoso Cantalice*[1], Carla Campos Muniz Medeiros[2], Jordana de Almeida Nogueira[3], Altamira Pereira da Silva Reichert[3], Inês Fronteira[4], Neusa Collet[3], Fernanda Lucia da Silva[1], Allana Petrúcia Medeiros de Miranda[1]

[1]Federal University of Campina Grande. Cuité - Paraíba, Brazil; [2]Paraiba State University. Campina Grande – Paraíba, Brazil; [3]Federal University of Paraíba. João Pessoa– Paraíba, Brazil; [4]Global Health and Tropical Medicine, Institute of Hygiene and Tropical Medicine, New University of Lisbon. Lisbon, Portugal

ARTICLE INFO

Article History:
Received 17th July, 2020
Received in revised form
12th August, 2020
Accepted 08th September, 2020
Published online 30th October, 2020

Key Words:
Metabolic Syndrome X. Obesity. Risk Factors. Children. Adolescent.

Corresponding author:
Anajás da Silva Cardoso Cantalice

ABSTRACT

Introduction: Confirmation of new markers that relate to metabolic syndrome evidence of cardiovascular disease prevention possibilities. Persistent metabolic syndrome is associated with new cardiovascular risk factors in children and adolescents are overweight or obese. **Materials and Methods:** Study of repeated measurements performed on Childhood Obesity Center April / 2009 to April / 2012, involving 133 children and adolescents. The evaluation took place at first and after 24 months. In both evaluations were performed anthropometry and diagnosis of metabolic syndrome, the second time the persistence of the syndrome was identified and then was verified its relationship with the new risk markers [fibrinogen, C-reactive protein ultrasensitive (CRP) , homocysteine and lipoprotein (a)]. **Results:** We observed persistence of the syndrome in 17.3% of evaluated. There was a positive correlation between homocysteine with waist circumference (p = 0.04) and negatively with HDL-C (p = 0.04) and positive of us-CRP with waist circumference (p = 0.01). **Conclusions:** Persistent metabolic syndrome was not associated with new cardiovascular risk markers, however there was positive correlation between the levels of hsCRP and homocysteine with waist circumference, negative relationship between HDL-C and hsCRP with lipoprotein (a) with waist circumference.

Citation: ***Anajás da Silva Cardoso Cantalice, Carla Campos Muniz Medeiros, Jordana de Almeida Nogueira, Altamira Pereira da Silva Reichert, Inês Fronteira, Neusa Collet, Fernanda Lucia da Silva, Allana Petrúcia Medeiros de Miranda. 2020.*** "Persistent metabolic syndrome and new cardiovascular risk markers in overweight or obese children and adolescents*", International Journal of Development Research*, 10, (10), 41306-41311.

INTRODUCTION

Current epidemiological evidence shows pandemic proportions of cardiovascular diseases (CVD) and the number of people at high risk of developing these disorders is increasing. Studies have shown that only 2 to 7% of the general population does not have any cardiovascular risk factor, while over 70% of individuals present multiple factors [1,2]. The development of atherosclerosis, as evidenced by the presence of fatty streaks in the vascular endothelium, begins in childhood, in association with increasing adiposity, dyslipidemia and hypertension, and the additional effect of these factors has increased the risk of premature death in adulthood.

Given these associations and the increasing prevalence of obesity, including morbid obesity, demonstrated in three Brazilian surveys [3], the identification of children and adolescents at risk for cardiovascular disease becomes increasingly urgent[4]. The relationship between obesity and metabolic syndrome seems especially important in childhood because excess weight has been considered a predisposing factor for the development of risk factors, thus contributing to early endothelial dysfunction, which has been diagnosed in approximately 40% of obese children [5]. Study carried out with 458 American children and adolescents followed for 10 years to verify the type of metabolic syndrome in the transition to adulthood, showed that obese adolescents were more likely to develop persistent or intermittent metabolic syndrome [6]. Although still widely discussed, the most used concept of

metabolic syndrome (MS) in childhood consists of at least three of the risk factors considered traditional: increased waist circumference, high blood pressure, hypertriglyceridemia, high-density lipoprotein (HDL-C) and hyperglycemia [7], but new markers present in cardiovascular events have shown a close relationship with obesity and diagnosis of MS [8]. Prothrombotic factors involved in obesity interface, cardiovascular disease and endothelial dysfunction, such as inflammatory markers such as High Sensitivity C-Reactive Protein (hsCRP), coagulation factors such as fibrinogen and liver and plasma proteins such as lipoprotein (a) and homocysteine have emerged as promising tools for diagnosis, prognosis and therapeutic guidelines of individuals at risk[9]. In this context, the present study aims to evaluate the relationship between persi

MATERIAL AND METHODS

This is a cross-sectional study of repeated measurements performed at the Childhood Obesity Centre, reference service that treats overweight or obese children and adolescents referred by Basic Health Units. All children and adolescents aged 2-18 years who searched the service from April / 2009 to April / 2012 were considered as study population. The minimum sample size was estimated in 200 visits, based on a population of 65,890 children and adolescents aged 2-18 years registered on December 2008 in the primary care information system (SIAB) of Campina Grande. Prevalence of overweight and obesity of 25% [10] and MS of 42% in Brazilian children and adolescents with this condition was also considered [11], with 20% increase for possible losses. The selection of children and adolescents was based on convenience criteria, and their recruitment was done sequentially over the study period until reaching the minimum number required. Those who were excluded at the time of data collection were carriers of a chronic disease such as hypertension and diabetes or were on medications that interfere with glucose or lipid metabolism, such as corticosteroids. After 24 months of follow-up, the 133 children and adolescents who remained in the study were reassessed in relation to nutritional status and metabolic condition (Figure 1). Over two years, participants have gone through quarterly consultations with endocrinologist, nutritionist and physical trainer for the performance of physical examination, guidance on complications associated with overweight and about the practice of physical exercise and monthly by the nurse who performed anthropometric measurements. Children and adolescents recruited at the first moment who discontinued were called for reassessment. For participation in both stages of the study, parents / guardians were informed about the procedures and in case of agreement, they signed the Informed Consent Form (ICF). After implementation of the checklist for verification of the exclusion criteria on both moments, a form addressing demographic, socioeconomic issues (gender, age and income) was applied and anthropometric measurements and laboratory tests were performed. Anthropometric variables (weight, height and waist circumference) were observed in duplicate, being considered the average of the two measurements, according to recommendations of the World Health Organization (WHO) [12]. Nutritional status was classified according to body mass index (BMI), according to recommendations from the Centers of Disease Controland Prevention (CDC) as overweight (BMI ≥ 85th percentile and <95th percentile), obesity (BMI ≥ 95th percentile and <97th percentile) and severe obesity (BMI ≥ 97thpercentile) [13]. Waist circumference (WC) was considered increased when presenting values higher than or equal to the 90th percentile, according to the International Diabetes Federation (IDF) [14], with maximum of 88 cm for girls and 102 cm for boys, according to the National Cholesterol Education Program Adult Treatment Pannel III (NECP-ATPIII) [15], measured at the midpoint between the lateral iliac crest and the lower edge of the last rib, during expiration [16]. Blood pressure was measured by the oscillometric method with Tycos® equipment, according to rules established in the VI Brazilian Guidelines on Hypertension [17]. High-density lipoprotein (HDL-C), triglycerides (TG) and glucose were assessed by the enzymatic colorimetric method in automatic equipment (Model BioSystems 310), lipoprotein (a) was assessed by the method, homocysteine verified by enzyme immunoassay and determination of high hensitivity C-Reactive Protein (CRP) performed by chemiluminescence in IMMULITE 1000 automated equipment (SIEMENS®). Blood samples were collected after a 12-hour fasting period. The diagnosis of MS was carried out using criteria recommended by the NCEP / ATPIII and adapted to age group. The presence of at least three of the following criteria, according to the NCEP / ATPIII was considered: WC above or equal to the 90th percentile for gender, age and race; Triglycerides ≥ 100 mg/dLnand / or HDL-$_C$<45 mg / dL, fasting glucose ≥100mg / dL, systolic and / or diastolic pressure above or equal to the 90th percentile for sex, height and age. The diagnosis of MS was verified in two moments and divided into two groups: negative or intermittent MS, individuals who have never had or had diagnosis of MS in one of the following points and persistent MS was diagnosed in individuals who were diagnosed with MS in both assessments. New cardiovascular risk markers were considered according to the III Brazilian Guidelines on Dyslipidemia: lipoprotein (a) with values equal to or greater than 30 mg / dL [19], homocysteine and fibrinogen levels, as there is no cutoff point to the child population and hs-CRP above 3 mg / dL excluding values equal to or greater than 10 mg / L for suggesting acute infectious or inflammatory process [20]. To verify the normality of variables, the Kolmogorov-Smirnoff test was applied. Data were presented as proportions, means and standard deviations (SD) for variables with normal distribution and median and interquartile interval for variables that are not normally distributed. Comparisons of the first moment and after 24 months of the frequencies of variables (BMI, WC, systolic and diastolic blood pressure, triglycerides, HDL-C, fasting blood glucose and hsCRP) were performed by the McNemar test. To perform the comparison of means of hsCRP and MS components at the end of the assessment according to the persistence or not of MS, the Student t test was used for the median of the other cardiovascular risk markers (lipoprotein (a), fibrinogen and homocysteine), as well as the Mann-Whitney test. Spearman correlation between the new cardiovascular markers and MS components was also performed (Altman, 1991). All analyses were performed with the SPSS software version 17.0 (SPSS Inc, Chicago, USA), considering a significance level of 5%.This study was approved by the Ethics Research Committee of the Paraíba State University through CAAE nº. 0040.0.133.000-08.

RESULTS

Biological, clinical and laboratory characteristics of 133 children and adolescents evaluated are shown in Table 1. Persistent MS occurred in 17.3% of children and adolescents evaluated, with significant reduction of prevalence after 24 months (p = 0.02).

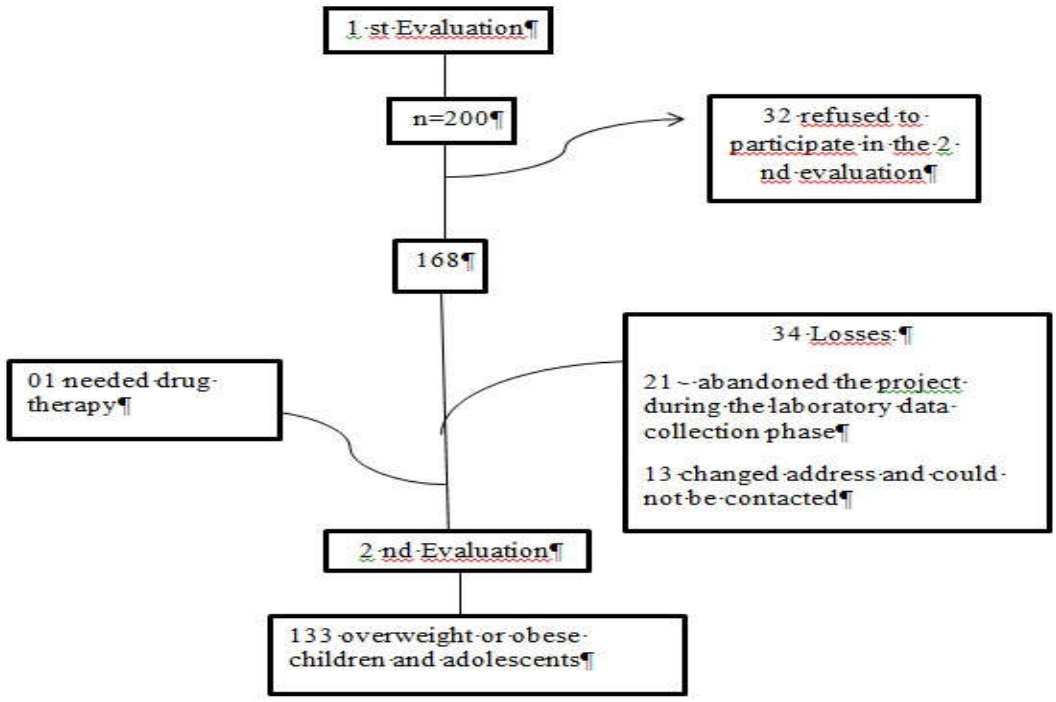

Figure 1. Flowchart of losses during the 24-month evaluation

Table 1. Sample Characterization during the evaluation period. Childhood Obesity Centre, Campina Grande - Paraíba, 2009- 2012

Variables	T_0 n (%)	$T_{24\ months}$ n (%)	Persistence of components n (%)	*p*
Sex			-	
Male	52 (39.1)			
Female	81 (60.9)			
Age Group(2012)				
Childhood	53 (39.9)	30 (22.6)		
Adolescence	80 (60.1)	103 (77.4)		
Income				
≤ 2 minimum wages	71 (53.4)	-		
>2 minimum wages	62 (46.6)	-		
Nutritional Status			76 (57.1)	0.32
Severe obesity	91 (68.4)	85 (63.9)		
Overweight / Obesity	42 (31.6)	44 (33.1)		
Normal weight	-	4 (3.0)		
High waste circumference	86 (64.7)	94 (70.7)	74 (56.1)	0.28
Hypertriglyceridemia	47 (35.6)	54 (40.6)	29 (22.1)	0.36
Low HDL (mg/dL)	105 (79.5)	117 (89.3)	96 (73.8)	0.06
High systolic pressure (mmHg)	49 (36.8)	12 (9.1)	6 (4.5)	<0.01
High diastolic pressure (mmHg)	86 (64.7)	42 (31.8)	32 (24.2)	<0.01
Fasting hyperglycemia	2 (1.5)	1 (0.8)	1 (0.8)	1.00
MS diagnostic	50 (38.2)	33 (25.8)	22 (17.3)	0.02
Hs-PCR	47 (40.9)	48 (38.4)	22 (20.8)	0.868

HDL - High Density Lipids; SBP - systolic blood pressure; DBP - diastolic blood pressure; MS - Metabolic Syndrome; hsCRP - High Sensitivity C-Reactive Pro

Table 2: Demographic characteristics, MS components and new cardiovascular risk markers at the end of the evaluation period according to MS persistence. Childhood Obesity Centre, Campina Grande - Paraíba, 2009- 2012

	MS persistence		
Variables	Present Mean (±SD)	Absent Mean (±SD)	*P*
Age	11.6 (3.69)	13.2 (3.71)	0.06
Income (R$)	1312.8 (687.84)	1505.3 (1423.21)	0.53
BMI	30.2 (5.77)	29.3 (6.00)	0.49
Waist circumference (cm)	90.8 (13.53)	88.3 (12.23)	0.40
Triglycerides (mg/dL)	164.9 (98.56)	130.4 (71.54)	0.05
HDL (mg/dL)	34.7 (6.23)	35.2 (9.50)	0.80
Systolic BP (mmHg)	113.2 (9.18)	107.0 (10.26)	0.01
Diastolic BP (mmHg)	79.9 (5.73)	71.5 (8.12)	<0.01
Fasting blood glucose (mg/dL)	82.1 (9.77)	79.8 (9.21)	0.30
HsCRP	2.9 (2.07)	3.0 (3.79)	0.95

HDL - High Density Lipids; SBP - systolic blood pressure; DBP - diastolic blood pressure; hsCRP - High Sensitivity C-Reactive Protein.

Table 3: Correlation of MS components according to new cardiovascular risk markers at the end of the evaluation period according to the MS persistence. Childhood Obesity Centre, Campina Grande - Paraíba, 2009- 2012

Variables	Fibrinogen *r*	*p*	HCY *r*	*P*	Lipo (a) *r*	*P*	hsPCR *r*	*p*
Waist circumference	0.07	0.41	0.17	0.04	-0.16	0.05	0.21	0.01
Triglycerides	0.08	0.37	-0.10	0.26	-0.02	0.81	0.07	0.41
HDL-c	-0.12	0.19	-0.17	0.04	0.01	0.88	-0.14	0.12
Fasting blood glucose	0.10	0.25	-0.03	0.69	-0.08	0.32	-0.06	0.51

Among MS components, only systolic and diastolic blood pressure were significantly reduced ($p < 0.01$). There was also a reduction of severe obesity (percentil≥97) with appearance of normal weight individuals (3%). The component that showed higher prevalence of persistent MS was low HDL-c (Table 1). Significant difference in mean triglyceride levels ($p = 0.05$), systolic ($p = 0.01$) and diastolic blood pressure ($p < 0.01$) among participants with persistent MS compared to those without the syndrome (Table 2). However, this relationship has not been verified with mean fibrinogen, homocysteine and lipoprotein values (a) (Figure 2). Among the MS components, there was positive correlation between waist circumference with homocysteine ($p = 0.04$) and hsCRP ($p = 0.01$) and low HDL-c with homocysteine ($p = 0.04$) (Table 3).

DISCUSSION

Since MS is composed of known risk factors, in which the effect of different factors is synergistic, multiplicative and amplifies, to a considerable extent, the risk for cardiovascular events, the confirmation of new markers related to this syndrome shows possibilities of preventing these outcomes [21]. In this sense, this research points out the relationship between new cardiovascular risk markers and MS persistence in overweight or obese children and adolescents. Although they have been studied separately, metabolic and immune pathways in the human body are interdependent, as hormones, cytokines and signaling proteins act on both routes aiming at homeostasis[22]. In this study, there was no relationship of fibrinogen, homocysteine, hsCRP or lipoprotein (a) directly with the MS persistence, but with some of its components. Fibrinogen, an acute phase protein, is part of the group of inflammatory biomarkers produced by hepatocytes and considered an important marker to monitor the progress of the atherosclerotic inflammatory process [23]. The relationship with MS is explained by the increase of its synthesis in response to chronic inflammatory events present in obesity, a common outcome of this syndrome [24].

Study with 241 French children showed association between increased fibrinogen levels and fat mass percentage and higher number of cardiovascular risk factors [25], corroborating research carried out with Asian obese children points positive correlation between fibrinogen and BMI, Triglycerides, Total Cholesterol, LDL-C and fasting insulin and negative with HDL-c [26]. Homocysteine levels (amino acid derived from methionine) have been linked to increased risk of premature coronary artery disease, stroke, and thromboembolism, even in individuals who do not have classical risk factors like dyslipidemia. Abnormal homocysteine levels appear to contribute to atherosclerosis due to the following reasons: (1) direct toxic effect that damages cells covering the inner side of the arteries, (2) interference with clotting factors, and (3) oxidation of low density lipoproteins (LDL)[27]. A survey with 1,000 Nepalese children and adolescents found association between elevated homocysteine levels and increased risk of metabolic syndrome from logistic regression models adjusted for sex [28]. Study with 540 Brazilian children and adolescents also points relationship between hyperhomocysteinemia and MS, as well as blood pressure and weight [29]. This study also found a positive correlation of hsCRP and homocysteine with waist circumference, negative correlation of hs-PCR and $HDL\text{-}_C$ and lipoprotein (a) with waist circumference. The first suggestion for a possible connection of hsCRP with atherosclerosis came with the observation that the protein selectively binds to the low density lipoprotein (LDL-C). It is speculated hsCRP can have significant pro-inflammatory effects and that when binding to molecules exposed on the cells (resulting from infection, inflammation, ischemia and other diseases) and trigger complement activation, it can exacerbate tissue damage, reflecting increased formation of atherosclerotic plaques, higher tendency to plaque rupture and thrombosis [30]. A study carried out with 80 obese Kuwaiti adolescents showed positive correlation of hsCRP levels with BMI and waist circumference [31], in accordance with Cardiovascular Health Study, which also highlights this association, indicating that although there is no single cutoff point, children and adolescents included in the study had subclinical inflammation associated with obesity and visceral adiposity [32].

A longitudinal study carried out for 3 years with overweight children and adolescents aged 8-13 years in Latin America showed that persistent metabolic syndrome was significantly associated with high carotid intima-media thickness, as well persistence of high waist circumference, showing the atheroschlerotic potential of metabolic alterations for prolonged periods [33]. As for lipoprotein (a), results have shows its double atherogenic character due to the fact that it has lipid composition similar to that of LDL-c and the presence of apolipoprotein (a) in its structure, which has a high degree of homology with plasminogen. When evaluating its relationship with BMI in the pediatric population, divergent results are obtained [8]. Study of young people presenting obesity, hypertension and diabetes showed significant changes in lipid metabolism, particularly for total cholesterol, LDL-c, the triglycerides, lipoprotein (a) and apolipoprotein A levels (Apo A) and Apo B[34]. However, similarly to results observed in this study, studies evaluating obese children and african-American adolescents found a negative correlation with BMI and waist circumference, emphasizing that increased plasma levels of lipoprotein (a) is not an independent risk factor for cardiovascular diseases[35]. Given the above, it appears that the classic risk factors for cardiovascular diseases do not fully explain cardiac outcomes, keeping the interest of many researchers in the biochemical and nutritional factors involved in the pathophysiology of the vascular disease[36]. The sample loss (21.8%) in the evaluation period was similar to other studies with obese or overweight young people [6]. Some factors may have contributed to these losses, for example, difficulty in commuting, since many children needed public transportation

and the project does not have resources to control this difficulty; and the need for the presence of a responsible person to lead the child to the place of intervention.

Conclusions

This study has important implications for screening of overweight or obese children and adolescents, pointing to new cardiovascular risk markers associated with a group of persistent metabolic disorders. However, given the complexity and multifactorial origin of cardiovascular diseases, studies with broader population groups randomized and with cross-sectional design are necessary to understand the impact of these markers on cardiovascular health, as well as for real need for inclusion of obese individuals in evaluation protocols. Persistent MS showed not associated with new cardiovascular risk markers under analysis [fibrinogen, homocysteine, hsCRP and lipoprotein (a)]. However, there was a positive correlation of hsCRP levels and homocysteine with waist circumference and negative correlation of homocysteine with HDL-$_C$ and lipoprotein (a) with waist circumference. Understanding the cascade of metabolic and immune alterations related to cardiovascular diseases is an important tool for early diagnosis and health promotion.

REFERENCES

Dahlof B. Cardiovascular disease risk factors: epidemiology and risk assessment. The American journal of cardiologyl. 2010; 105 (1): 3A-9A. DOI: doi.org/10.1016/ j.amjcard.2009.10.007.

Petersen LC, Hosanna H, Saldanha C, Basso M, Garcia P. Cardiovascular risk factors and comorbidities in cardiology clinics in the metropolitan region of Porto Alegre, RS. Magazine AMRIGS 2011; 55 (3): 217-223 .

Brazilian Institute of Geography and Statistics (IBGE). Consumer Expenditure Survey (POF) 2008-2009. Brasil, 2010.

Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. N Engl J Med. 2010; 362:485-493.

Stanley TL, Chen ML, Goodman E. The Typology of Metabolic Syndrome in the Transition to Adulthood. J Clin Endocrinol Metab. 2014 Mar; 99 (3): 1044-1052 .

Poet LS, MFS Duarte, Caramelli B, J Mota, Giuliano ICB. Effects of physical exercise and nutritional guidance on the cardiovascular risk profile of obese children. Rev. Assoc. Med Bras. 2013; 59 (1): 56-63 .

Silva LR, Stefanello JMF, Pizzi J, Timossi LS, Milk N. Subclinical atherosclerosis and inflammatory markers in children and obese and non-obese adolescents. Rev. bras. Epidemiol 2012; 15 (4): 804-16.

Palmeira AC, Leal AAF, MNM Ramos, F.Neto, JA, Simões MOS, Medeiros CCM. Lipoprotein (a) and cardiovascular risk factors in children and adolescents. Rev Paul. Pediatr 2013; 31 (4): 531-7

Pittan OMO, Barbisan JN. New inflammatory biomarkers and endothelial dysfunction, cardiovascular risk prediction. Magazine AMRIGS 2014; 58 (1): 69-77.

Silva MEM. et al. Prevalence of cardiovascular risk factors in children and adolescents in the school system of the city of Maceio. Arq. Bras. Cardiol 2005; 84 (5): 2573-81

Buff CG. et al. Frequency of metabolic syndrome in children and adolescents with overweight and obesity. Rev. paul. Pediatr 2007; 25 (3): 221-26 .

World Health Organization: The World Health Report 2002: Reducing risks, Promoting healthy life. Geneva, Switzerland in 2002.

Centers for Disease Control and Prevention (CDC). Table is calculated body mass index values for selected highs and weights for ages 2 to 20 years. Developed by the National Center for Health Statistc in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000. Published in May 2002 modified 20/04/2001. Available at: htpp: //www.cdc.gov/growthcharts. Port 20 de October 2014.

International Diabetes Federation (IDF) Worldwide Definition of Metabolic Syndrome Available at: http: //www.idf.org/home/index.cfm node = 1429? Accessed on October 20, 2014

Third Report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final report. Circulation 2002; 106: 3143-3421 .

American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33 (1).:62-69 .

Brazilian Society of Cardiology. VI Brazilian Guidelines on Hypertension. Arq Bras Cardiol. ISSN-1809-4260. 2010: 13, Volume 13, Number 1.

Giuliano ICB, Caramelli PBL. Brazilian Society of Cardiology. I Atherosclerosis Prevention Guidelines in Childhood and Adolescence. Arq Bras Cardiol 2005; 85: 1-36

Brazilian Society of Cardiology (SBC). III Brazilian Guidelines for dyslipidemia and Atherosclerosis Prevention Guideline of the Department of Atherosclerosis of the Brazilian Society of Cardiology. Arq Bras Cardiol 2001; 77 (Suppl III); 1-48

Ford ES. C-reactive protein concentration and cardiovascular disease risk factors in children: findings from the National Health and Nutrition Examination Survey 1999-2000. Circulation 2003; 108: 1053-8.

Farmer MSF, Abbes PT, Taddei JAAC. Cardiovascular Risk in Adolescents with Different Degrees of Obesity. Arq Bras Cardiol 2011; 96 (3): 205-11.

Vellosa JCR, Parabocz GC, Manente FA, Ribas JT, Lima LW. Metabolic and inflammatory changes in oxidative stress conditions. Rev Farm Ciênc Basic Appl, 2013; 34 (3): 305-312.

Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyzes of prospective studies. JAMA. 1998; 279: 1477-82.

Damiani D, Kuba VM, Cominato L, Dichtchekenian V, Menezes Filho HC. Metabolic syndrome in children and adolescents: questions of terminology, but not in cardiometabolic risk. Arq Bras Endocrinol Metab. 2011; 55 (8): 576-582

Bouglé D, Zunquin G, B Sesboué, Sabatier JP. Relationships of Cardiorespiratory Fitness with Metabolic Risk Factors, Inflammation, and Liver transaminases in Overweight Youths, "International Journal of Pediatrics 2010; 10: 1-5

Galli-Tsinopoulou A, Kyrgios I, Maggana I, Giannopoulou EZ, Kotanidou EP, Stylianou C, Papadakis E, Korantzis I, Varlamis G. Insulin resistance is associated with at least threefold Increased risk for prothrombotic state in

severely obese youngsters. Eur J Pediatr. 2011 Jul; 170 (7): 879-86.

Pizzi J, Silva LRMD, Milk N. Relationship between subclinical atherosclerosis, blood pressure and lipid profile in obese children and adolescents: a systematic review. Arq Bras Endocrinol Metab. 2013; 57 (1).

Yakub M, Schulze KJ, Khatry SK, Stewart CP, Christian P, West Jr KP. High Plasma Homocysteine Increases Risk of Metabolic Syndrome in 6 to 8 Year Old Children in Rural Nepal. Nutrients. Apr 2014; 6 (4): 1649-1661

Pitangueira JCD, Silva LR, Santana MLP, Silva MCM, Costa PRF, D'Almeida V, Assis AMO. Metabolic syndrome and associated factors in children and adolescents of a Brazilian municipality. Nutr Hosp. 2014 Apr 1; 29 (4): 865-72.

Miller M, Zhan M, Havas S. High attributable risk of elevated C-reactive protein level to conventional coronary heart disease risk factors: the Third National Health and Nutrition Examination Survey. Arch Intern Med 2005; 165 (18): 2063-8.

Dayal D, Jain H, Attri SV, Bharti B, AK Bhalla. Relationship of High Sensitivity C-Reactive Protein Levels to Anthropometric and other Metabolic Parameters in Indian Children with Simple Overweight and Obesity. J Clin Diagn Res.2014 Aug; 8 (8): PC05-8.

Emanuela F, Grazia M, Robertis M, Luconi MP, Furlani G, Boscaro M. Inflammation as a Link between Obesity and Metabolic Syndrome. J Nutr Metab. 2012 Mar .; 2012 (476380): 1-7

Toledo CM, Ventura EE, Hodis HN, Weigensberg MJ, Lane CJ, Li Y, Goran MI. Persistence of the metabolic syndrome and its influence on carotid artery intima thickness average in overweight Latino children. Atherosclerosis. 2009 Oct; 206 (2): 594-8

Glowinska B, Urban M, Koput A, Galar M. New atherosclerosis risk factors in obese, hypertensive and diabetic children and adolescents. Atherosclerosis 2003; 167: 275-86

Sharma S, Merchant J, Fleming SE. Lp (a) -cholesterol is associated with HDL-cholesterol in overweight and obese African American children and is not an independent risk factor for CVD. Diabetol Cardiovasc 2012; 11: 1-7.

Ghisi GLM, Durieux A, Pine R, Benetti M. Physical exercise and endothelial dysfunction. Arq. Bras. Cardiol 2010; 95 (5): 130-137.

****