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Cardiovascular lesions in children with obesity

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Abstract

The dominance of cardiovascular diseases in the structure of mortality and disability in developed countries as well as the increasing incidence of cardiovascular disorders led to development of conception of cardiovascular continuum based on the clinical evaluation of the risk factors for cardiovascular complications. In this regard studying of the initial stages of this process, i. e. childhood and adolescence, is of great interest. It is now apparent that childhood obesity may be regarded as a cardiovascular risk factor in adulthood. This fact also corresponds to the accumulated information on the cardiovascular disease in children and adolescents with obesity and its similarity with the changes found in adults. What also facilitates the importance of this issue is a steady worldwide increase of the percentage of infants with excess body weight, which may lead to possible increase in cardiovascular disease in the near future. The review covers early manifestations of cardiovascular disease in children with obesity, the development of endothelial dysfunction, remodeling of the artery wall and the progression of atherosclerotic lesions in the aorta and peripheral vessels. The review addresses the distinction of the hypertension development and course as well as the indication of cardiac remodeling and diagnostic criteria of left ventricular hypertrophy. The review provides directions in prevention and treatment of cardiovascular changes in children and adolescents with obesity.

Key words: children, adolescents, obesity, cardiovascular system, early diagnosis

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Поражения сердечно-сосудистой системы у детей с ожирением

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Резюме

Доминирующая доля сердечно-сосудистых заболеваний в структуре смертности и инвалидизации населения развитых стран, рост сердечно-сосудистой патологии привели к формированию представления о сердечно-сосудистом континууме, основанном на клинической оценке факторов, влияющих на риск развития сердечно-сосудистых осложнений. В связи с этим актуальным является изучение начальных этапов этого процесса, а именно — детства и подросткового периода. В настоящее время стало очевидным, что ожирение у детей может рассматриваться как фактор сердечно-сосудистого риска в последующие зрелые годы. Такому взгляду способствуют накопившиеся сведения о поражении сердечно-сосудистой системы у детей и подростков с ожирением и их созвучность изменениям, обнаруживаемым у взрослых. Актуальности этого вопроса способствует и тот факт, что во всем мире наблюдается неуклонный рост доли детей с избытком массы тела, что может означать возможное увеличение сердечно-сосудистой патологии в недалеком будущем. В обзоре освещены ранние проявления поражения сердечно-сосудистой системы у детей с ожирением. Обсуждаются развитие эндотелиальной дисфункции, процессы ремоделирования артериальной стенки, возникновение атеросклеротических повреждений в аорте и периферических сосудах. Также уделено внимание особенностям развития и течения артериальной гипертензии, рассмотрены признаки ремоделирования сердца и критерии диагностики гипертрофии миокарда левого желудочка. Приведены направления профилактики и лечения кардиоваскулярных изменений у детей и подростков с ожирением.

Ключевые слова: дети, подростки, ожирение, сердечно-сосудистая система, ранняя диагностика

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Introduction

At present the major biological factors of cardiovascular diseases are arterial hypertension (HTN), high blood cholesterol level, type 2 diabetes mellitus and obesity. The epidemiological and biological risks of cardiovascular diseases are known to form in childhood, so the increasing rate of excess body weight among children is a warning signal of possible growth of cardiovascular complications in the near future. This fact

demonstrates the need of detection and correction of the earliest signs of obesity-related cardiovascular damage [1].

Endothelial dysfunction, arterial remodeling, atherosclerotic arterial lesions

In recent years, it became clear that the violation of the dilation endothelial function is the trigger of some cardiovascular disorders, occurring in obesity, especially in insulin resistance. Endothelium-dependent arterial dilatation was shown to be dependent on a number of vasodilating factors, and nitric oxide (NO) plays the key role. In obesity, which is accompanied by a long-term hemodynamic arterial overload and hyperactivation of the renin-angiotensin system (RAS) and sympathetic nervous system (SNS), endothelium-dependent NO synthesis decreases and endothelial dysfunction (ED) develops.

Several longitudinal prospective studies showed that endothelium-dependent vasodilatation is inversely associated with the increased risk of cardiovascular events not only in the elderly [2, 3], but also in middle-aged people without obvious heart diseases [4]. Some authors suggest that the ED detection may be considered as an early diagnostic sign of the cardiovascular continuum onset [5, 6]. Based on the studies of the endothelium-dependent arterial dilatation in obese children, ED is found in half of overweight children and adolescents [7–15]. There was a significant inverse correlation between the degree of arterial dilatation in postocclusion hyperemia test and body mass index (BMI) even in children with normal body weight [5].

ED eventually leads to the remodeling of vascular wall, which is accompanied by a thickening of the so-called complex "intima-media" (IMC). This phenomenon is accompanied by the reduction of elastic properties of main and peripheral arteries. The IMC thickening in adults was found to be associated with the development of atherosclerotic plaques in carotid arteries, as well as in other peripheral arteries [16]. Herewith, it is shown that IMC thickening is associated with the increased risk of cardiovascular diseases and their acute complications (coronary heart disease, peripheral artery disease, stroke, myocardial infarction) [17–19].

The direct correlation between the IMC thickening in childhood and the thickness of the arterial wall in adults has been demonstrated in a well-known prospective study (Bogalusa Heart Study). In this study 1142 people were examined several times throughout their lives, from 2 to 43 years old [20]. As it turned out, high IMC thickness in overweight children also persisted further in adulthood. Also a number of studies demonstrated carotid artery wall thickening in children with obesity associated with hypertension and insulin resistance,. It was accompanied by the reduction of the brachial artery relaxation to reactive hyperemia [21–25]. Multivariate analysis of the data obtained during examination of obese children aged 9–13 years demonstrated that the IMC carotid artery thickness significantly correlated with systolic blood pressure (BP), fasting glucose level and BMI [22]. According to Toledo-Corral C. et al. from Latin America, IMC thickening is more common in children with metabolic syndrome than in children with obesity but without insulin resistance [26].

The vascular wall remodeling in response to hemodynamic overload, impaired insulin resistance, increased blood pressure possibly promotes atherosclerotic lesions of the intima, and it can start already in childhood. It is especially intensive in obesity, often associated with atherogenic lipid profile in addition to the adverse hemodynamic changes. The results of another prospective study (Muscatine Study) of 14000 children followed-up for 20 years, showed that maximum thickness of carotid artery IMC at the age of 42 years old was observed in those people who had the low-density lipoprotein cholesterol level in the upper percentile in childhood (8–11 years) [27]. Authors of this study consider the increased IMC thickness in childhood as an early marker of atherosclerotic vascular damage. In the project "Pathobiological atherosclerosis determinants in youth"the intima of the aorta and coronary arteries of children and adolescents died from accidents was investigated. The data indicate that fibrous plaques in the aorta were found in 19% of children died between 2 and 15 years old, and the similar lesions in the coronary arteries were found in 35% in the group of adolescents of 16–20 years old [28].

In another study, including an autopsy data of 1154 people who died at 15 to 34 years old, there was a correlation between the severity of

the right coronary artery intima lesion and the thickness of adipose umbilical fold [29]. The severity of atherosclerotic coronary artery lesions was associated with the fat fold thickness and BMI in males.Atherosclerotic vascular lesions usually are associated with several damaging factors. Thus, analysis of the autopsy material in casualties occurred at the age of 2–39 years old showed that BMI, systolic blood pressure, the low-density lipoprotein cholesterol and triglyceride levels (taken as a value above the 75th cutoff point level adjusted for race, gender and age) were significantly associated with the extent of adipose and fibrous plaques in the aorta and coronary arteries. The correlation coefficient between the affected area of the coronary arteries and studied risk factors was 0.55 for adipose plaques and 0.52 for fibrous [30]. In other words, if there are 3 or 4 risk factors, the area of adipose lesions of the coronary arteries intima was 8.5 times larger and the area of fibrous plaques was 12 times larger compared to subjects without known risk factors during their lifetime [20]. The authors concluded that the extension of atherosclerotic lesions in the aorta and coronary arteries in children and young adults significantly increases depending on the number of risk factors.

Arterial hypertension

Arterial hypertension is frequently associated with obesity, also in childhood. According to the actual concept, the key factors for blood pressure elevation are insulin resistance and insulin level increase leading to SNS hyperactivation, which in turn stimulates vascular tone, heart and activates the RAS.

Leptin which promotes increase in adrenocorticotropic hormone, cortisol and aldosterone levels may also contribute SNS stimulation [31].

Recent studies indicate an important role of inflammatory reactions and immune system activation in the development of insulin resistance and associated conditions, such as diabetes mellitus, central obesity, arterial hypertension, atherosclerosis. There are also similar data for overweight children [32–34]. Thus, obese children and adolescents have elevated serum concentrations of C-reactive protein, interleukin-6, interleukin-1β and intercellular adhesion molecule-1 which correlated with the blood pressure level at ambulatory BP monitoring [35]. Children with severe hypertension also have high levels of some prostaglandins (ISO 2α, CRP, ICAM-1 and VCAM-1) and tumor necrosis factor-α [36]. The C-reactive protein concentration in obese children was found to correlate with the IMC thickness [37], arterial stiffness [38], left ventricular hypertrophy [39] and BP level [40]. It was shown that inflammatory markers are present in obese subjects without BP elevation; however, the highest levels of these markers are found in co-morbid obesity and hypertension [41].

Obesity associated with low birth weight is thought to significantly increase the risk of hypertension. The highest systolic blood pressure was found in low birth weight babies who became obese later [42]. In addition, there can be even a prenatal predisposition to obesity and HTN, as was shown by Filler G. and colleagues [43]. In their study higher BMI levels in pregnant women were associated with the risk of obesity and BP increase in their children.

The rate of high BP in children significantly depends on the body mass, as demonstrated in a considerable number of studies [44–51]. In children and adolescents with BMI below the 85th percentile the frequency of high BP is 2.6%, while in children with BMI greater than the 95th percentile, it is 10.7% [52]. Bogalusa Heart Study showed higher systolic BP in children with body weight within the upper percentile of the body mass distribution in children population. During follow-up there was a disproportionate increase in systolic BP in this group compared to children with normal body weight [46]. Recent studies have shown that BP increase in children is closely related to the growth of body weight similar to a dose-dependent effect [49, 50]. Based on the retrospective analysis of the multicenter projects carried out in northern California, involving more than 117000 children aged from 6 to 17 years, 10% of obese children with BMI within 100–109% of the 95th percentile had elevated BP level, while the rate was 24% among children with severe obesity (BMI greater than the 95th percentile for 40% or more) [53].

Obese children with normal (according to office measurements) BP levels have higher daytime and nighttime systolic and diastolic BP according to ambulatory BP monitoring, as well as higher percentage of measurements exceeding the BP

threshold (hypertension load) than in the control group [54, 55].

In co-existent hypertension and obesity, there is a similar pattern in the dynamics of interval BP parameters. Thus, the maximal, and average daytime and nighttime BP values are significantly higher in children with obesity-related hypertension than in children with normal weight and clinically primary HTN [56, 57]. According to these authors, in individual obese adolescent maximal daytime systolic BP can increase up to 220–240 mm Hg, and diastolic BP — up to 150 mm Hg. Analysis of the hypertensive load in children with different body weight and HTN showed that intensity and resistance of HTN depend on BMI: stable HTN is verified in 60 % of obese children, in 36 % of overweight children and only in 27 % of children with normal body weight and elevated BP level [56]. These results are consistent with data by Bekezin VV et al. about relationship between the index HOMA-IR (Homeostasis Model Assessment of Insulin Resistance), reflecting insulin resistance, and the HTN resistance in obese children [58]. According to them, white-coat hypertension was predominant (70 %) in children with HOMA level below 2, while the labile and stable forms constituted 30 %. On the other hand, in obese children with high BP and HOMA index above 4, the rate of labile and stable forms of HTN reached 74 %.

Published data considering HTN forms in children and adolescents with high BP levels confirm that daytime systolic hypertension is the most common type [59, 60]. Moreover, the most common form of HTN in obese children is systolic-diastolic HTN, which can be registered throughout the day [56].

Nocturnal BP reduction in obese children is also of interest. It is known that there is a 10–20 % BP reduction at night compared with daytime level in healthy people (dipper). Now it is proved that inadequate BP reduction at night in hypertensive patients is directly related to target organ damage. For example, left ventricular hypertrophy which is an independent predictor of cardiovascular complications, is more frequently found in these patients.

BP reduction (dipper + over-dipper) at night was observed in 56 % of obese children, in 65 % of overweight children and in 72 % of children with normal body weight [56]. Insufficient BP reduction (non-dipper) is registered in approximately 30 % of children in each group. However, obese children more often demonstrated a BP increase at night time (night-peaker) compared to other groups, composing 11 % [56]. Regarding this, the highest left ventricular myocardial mass was registered in patients with hypertension and night-peaker BP profile. According to some authors, patients with HNT and abnormal nocturnal BP reduction have double risk of cardiovascular complications. They are also more likely to have cerebral stroke [61].

On the other hand, similar abnormal BP patterns (without abnormal reduction at night time) are also common in obstructive sleep apnea-hypopnea (OSAS) syndrome associated with upper airway obstruction. This syndrome is known to be the most common in obese people, and systemic HTN is one of the cardiovascular complications in this disorder [62]. Based on different studies, obstructive apnea is found in 46–59 % of obese children [63–65]. Obese children with moderate and severe OSAS are at significantly greater risk of systemic HTN than children with mild OSAS [66].

Thus, obese children have abnormal circadian BP profile which is associated with the high risk of acute cardiovascular events, target organ damage and OSA.

Cardiac remodeling

Heart remodeling in obesity involves cavities, myocardium and also functional changes. Cardiac remodeling in overweight people includes increase of the cavities and myocardial hypertrophy. Thus, the Framingham study [67, 68] indicate that an increase in left ventricular mass is observed in obesity regardless of BP level.

Hemodynamic preload plays a key role for cardiac remodeling in overweight subjects. The circulating blood volume increases greater in obesity than in non-adipose body mass. A rise in hemodynamic preload due to increased blood inflow leads to the augmentation of cardiac output accompanied by the tonogenic extension of left ventricular cavity, and the increase of its wall tension [69]. These result in eccentric myocardial hypertrophy characterized by high ratios, namely radius/thickness of the left ventricular wall and volume/mass of the left ventricle. Daniels S et al. studied children at age 6–17 years old, and

demonstrated that 10 kg increase in adipose mass is accompanied by 5 g increase in left ventricular mass [70]. Myocardium thickening reduces the excessive tension of its fibers that allows of maintaining normal left ventricle contractility, but at the same time predisposes to the diastolic dysfunction development [71, 72]. The last one is due to the relative reduction in number of capillaries per unit of muscle tissue volume and aggravation of the oxygen diffusion in hypertrophied muscle fibers. Echocardiography with tissue Doppler imaging demonstrated significant changes in the longitudinal myocardial function of both ventricles in obese children with normal BP values. There was a decrease in peak systolic myocardium velocity of both ventricles in this group of children that may indicate a violation of systolic function of subendocardial myocardium layer [73]. Moreover, concomitant OSAS [74, 75] and a dilatation endothelial dysfunction can also promote the development of cardiac remodeling in obese children [76, 77]. Myocardial mass index (MMI) may be considered as a criterion of left ventricular hypertrophy in obese children, if the MMI is over 40g/$m^{2,7}$ in girls and over 45g/$m^{2,7}$ in boys [78]. The MMI is calculated as follows: MMI = LVMM/$height^{2.7}$ [79].

Cardiovascular prevention and management approaches

Prevention of cardiovascular complications in obese children is directly related to weight loss, which is the main aim of treatment. Therefore, weight loss is crucial for the control of cardiovascular risk factors. It involves not only dietary restrictionsbut also moderate regular exercise (RE). There are current substantiated recommendations for children and adolescents suggesting necessary parameters of RE expressed in the number of steps/day [80]. However, it is necessary to remember that obese children often are unable to do intense prolonged exercise because of the low load tolerance and thereby they can not greatly increase the exercise intensity. Only with better training RE can make a major contribution to weight loss. the The guidelines of Russian Scientific Society of Cardiology for diagnosis, treatment and prevention of hypertension in children and adolescents include data about kilocalories expenditure per minute for different types of household activities and sports [81].

Despite the light RE at first does not significantly affect BMI, simple regular exercises (3–4 times a week) are highly important for an obese child. The protective effect of moderate RE for cardiovascular system in adults with different degrees of cardiovascular risk is obvious. It is also true for obese children. Thus, according to Swiss researchers [82], 3-month RE (60 minutes three times a week) led to a significant reduction of systolic and diastolic BP in prepubertal obese children, and this effect was persisted after 2 years [83]. Another study, conducted among children aged 8–11 years, demonstrated a direct relationship between endothelium-dependent arterial dilatation and compliance with RE, that was especially strong in case of intense exercises (correlation coefficient was equal to 0.58) [84]. Researchers from Germany have shown that regular physical activity during 6 months (1 hour 3 times a week) was associated not only with the improvement of the arterial dilatation function, but also with a significant reverse remodeling of peripheral arteries (IMC thickness reduction) in adolescents aged 12–16 years [85]. There are interesting data about an increase in the number of endothelial progenitor cells in peripheral blood after RE. Endothelial progenitor cells are believed to be responsible for the vascular endothelium recovery and growth [86]; the decrease in their number was found to be associated with the first signs of endothelial dysfunction. At the same time, after 12 weeks of regular exercises the number of these cells significantly increased in overweight 12-year-old children [87].

There is often a tendency to tachycardia in obese children, which reflects the SNS hyperactivity. In this case, autogenic training and meditation can be helpful. American researchers [88] analyzed the cardiovascular parameters in adolescents aged 15–18 years who participated in the program of transcendental meditation mastering and practice in order to prevent HTN and other cardiovascular diseases. After 2 months of training (15 minutes twice a day) there was a significant reduction in single BP values and mean daily BP (compared to baseline level) in response to a series of stress tests. After 4 months of meditation practice there was a significant increase in the brachial artery endothelium-dependent dilatation in all participants.

The results of a 5-year prospective study conducted by Trushkina IV et al. indicate that the BMI reduction was associated with the improvement of circadian BP profile and a significant reduction in left ventricular myocardium mass, even without antihypertensive drugs in half of the obese adolescents with obesity-related HTN [89]. On the other hand, antihypertensive therapy per se without BMI reduction did not lead to the similar improvements in the daily BP profile and left ventricular MMI. Thus, the authors suggest that BMI reduction has a more pronounced effect on the central and peripheral hemodynamics than antihypertensive drugs.

Antihypertensive therapy is reasonable in children and adolescents with resistant HTN, especially when there is target organ damage. At the same time, there is a lack of scientific evidence regarding the use of antihypertensive drugs, their efficacy and safety and also their pharmacokinetics in children and adolescents. However, currently 5 basic groups of antihypertensive drugs are used in children and adolescents, and the doses are specified. They include angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, dihydropyridine calcium antagonists and thiazide diuretics. Detailed recommendations, intake regimen and dosages are described in the guidelines [81].

There is not yet enough evidence supporting the use of other antihypertensive drugs (non-dihydropyridine calcium antagonists, loop diuretics, potassium-sparing diuretics, α-blockers, vasodilators, centrally acting agents) in children.

Conclusion

In conclusion, the available evidence about cardiovascular damage in obese children indicates that the cardiovascular continuum onset can occur in childhood. This requires early diagnostics of cardiovascular involvement and the development of its effective prevention and treatment.

Conflict of interest

Authors declare no conflict of interest.

References

1. Edleeva AG, Khomich MM, Volkov NY, Leonova IA, Yuryev VV. Estimation of body composition as a way to identify predictors of the development of the metabolic syndrome in children. Preventive and Clinical Medicine. 2010;3–4:183–186 [in Russian]

2. Gokce N, Keaney JF Jr, Hunter LM, Watkins MT, Nedeljkovic ZS, Menzoian JO et al. Predictive value of noninvasive-lydetermined endothelial dysfunction for long-term cardiovascular events inpatients with peripheral vascular disease. J Am Coll Cardiol. 2003;41:1769–1775.

3. Yeboah J, Sutton-Tyrrell K, Mcburnie MA, Burke GL, Herrington DM. Crouse JR. Association between brachial artery reactivity and cardiovascular disease status in an elderly cohort: The cardiovascular health study. Atherosclerosis. 2008;197:768–776.

4. Shechter M, Issachar A, Marai I, Koren-Morag N, Freinark D, Shahar Y et al. Long-term association of brachial artery flow-mediated vasodilation and cardiovascular events in middle-aged subjects with no apparent heart disease. Int J Cardiol. 2009;134:52–58.

5. Järvisalo MJ, Rönnemaa T, Volanen I, Kaitosaari T, Kallio K, Hartiala JJ et al. Brachial artery dilatation responses in healthy children and adolescents. Am J Physiol Heart Circ Physiol. 2002;282: H87-H92.

6. Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A et al. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation. 2001;104:191–196.

7. Aggoun Y, Farpour-Lambert NJ, Marchand LM, Golay E, Maggio ABR, Beghetti M. Impaired endothelial and smooth muscle functions and arterial stiffness appear before puberty in obese children and are associated with elevated ambulatory blood pressure. Eur Heart J. 2008;29:792–799.

8. Peña AS, Wiltshire E, MacKenzie K, Gent R, Piotto L, Hirte C et al. Vascular endothelial and smooth muscle function relates to body mass index and glucose in obese and nonobese children. J Clin Endocrinol Metab. 2006;91:4467–4471.

9. Meyer AA, Kundt G, Steiner M, Schuff-Werner P, Kienast W. Impaired flow-mediated vasodilation, carotid artery intima-media thickening, and elevated endothelial plasma markers in obese children: the impact of cardiovascular risk factors. Pediatrics. 2006;117:1560–1567.

10. Skilton MR, Celermajer DS. Endothelial dysfunction and arterial abnormalities in childhood obesity. Int J Obes. 2006;30:1041–1049.

11. Woo KS, Chook P, Yu CW, Sung RY, Qiao M, Leung SS et al. Effects of diet and exercise on obesity related vascular dysfunction in children. Circulation. 2004;109:1981–1986.

12. Tounian P, Aggoun Y, Dubem B, Varille V, Guy-Grand B, Sidi D et al. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. Lancet. 2001;358:1400–1404.

13. Meyer AA, Kundt G, Lenschow U, Schuff-Werner P, Kienast W. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. J Am Coll Cardiol. 2006;48:1865–1870.

14. Singhal A. Endothelial dysfunction: role in obesity-related disorders and the early origins of CVD. Proc Nutr Soc. 2005;64:15–22.

15. Aggoun Y, Szezepanski I, Bonnet D. Noninvasive assessment of arterial stiffness and risk of atherosclerotic events in children. Pediatr Res. 2005;58:173–178.

16. Bonithon-Kopp C, Touboul PJ, Berr C, Leroux C, Mainard F, Courbon D et al. Relation of intima-media thickness to atherosclerotic plaques in the carotid arteries: the Vascular Aging (EVA) Study. Arterioscler Thromb Vasc Biol. 1996;16:310–316.

17. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999;340:14–22.

18. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol. 1997;146:483–494.

19. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Predictionof clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007;115:459–467.

20. Raghuveer G. Lifetime cardiovascular risk of childhood obesity. Am J Clin Nutr. 2010;91(5):1514S-1519S.

21. Kapiotis S, Holzer G, Schaller G, Haumer M, Widhalm H, Weghuber D, et al. A proinflammatory state Isdetectable in obese children and is accompanied by functional and morphological vascular changes. Arterioscler Thromb Vasc Biol. 2006;26:2541–2546.

22. Reinehr T, Kiess W, de Sousa G, Stoffel-Wagner B, Wunsch R. Intima media thickness in childhood obesity: Relations to inflammatory marker, glucose metabolism, and blood pressure. Metabolism. 2006;55:113–118.

23. Karpoff L, Vinet A, Schuster I, Oudot C, Goret L, Dauzat M et al. Abnormal vascular reactivity at rest and exercise in obese boys. Eur J Clin Invest. 2009;39:94–102.

24. Urbina EM, Kimball TR, McCoy CE, Khoury PR, Daniels SR, Dolan LM. Youth With obesity and obesity-related type 2 diabetes mellitus demonstrate abnormalities in carotid structure and function. Circulation. 2009;119:2913–2919.

25. Dangardt F, Osika W, Volkmann R, Gan LM, Friberg P. Obese children show increased intimal wall thickness and decreased pulse wave velocity. Clin Physiol Funct Imaging. 2008;28:287–293.

26. Claudia Toledo-Corral, Emily Ventura, Marc Weigenberg, Howard Hodis, Yanjie Li, Michael Goran. Persistence of the metabolic syndrome and its influence on carotid artery intima media thickness in overweight Latino children. Atherosclerosis. 2009;206(2):594–598.

27. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid Intimal-Medial Thickness Is Related to Cardiovascular Risk Factors Measured. From Childhood Through Middle Age: The Muscatine Study, Circulation. 2001;104:2815–2819.

28. McGill HC Jr, McMahan CA, Malcom GT, Oalmann MC, Strong JP. Relation of glycohemoglobin and adiposity to atherosclerosis in youth. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol. 1995;15(4):431–440.

29. McGill HC Jr, McMahan CA, Malcom GT, Oalmann MC, Strong JP. Relation of glycohemoglobin and adiposity to atherosclerosis in youth: Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol. 1995;15:431–440.

30. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med. 1998;338:1650–1656.

31. Haynes WG. Role of leptin in obesity-related hypertension. Exp Physiol. 2005;90(5):683–688.

32. Lypez-Jaramillo P, Herrera E, Garcia RG, Camacho PA, Castillo VR. Inter-relationships between body mass index, C-reactive protein and blood pressure in a Hispanic pediatric population. Am J Hypertens. 2008;21:527–532.

33. Głowińska-Olszewska B, Tołwińska J, Urban M. Relationship between endothelial dysfunction, carotid artery intima media thickness and circulating markers of vascular inflammation in obese hypertensive children and adolescents. J Pediatr Endocrinol Metab. 2007;20:1125–1136.

34. Stumpf C, Jukic J, Yilmaz A, Raaz D, Schmieder RE, Daniel WG et al. Elevated VEGF-plasma levels in young patients with mild essential hypertension. Eur J Clin Invest. 2009;39:31–36.

35. Syrenicz A, Garanty-Bogacka B, Syrenicz M, Gebala A, Dawid G, Walczak M. Relation of low-grade inflammation and endothelial activation to blood pressure in obese children and adolescents. Neurol Endocrinol Lett. 2006;27:459–464.

36. Cottone S, Mulu G, Nardi E, Vadala A, Guarneri M, Briolotta C et al. Relation of C-reactive protein to oxidative stress and to endothelial activation in essential hypertension. Am J Hypertens. 2006;19:313–318.

37. Reinehr T, Kiess W, de Sousa G, Stoffel-Wagner B, Wunsch R. Intima media thickness in childhood obesity: relations to inflammatory marker, glucose metabolism, and blood pressure. Metab Clin Exp 2006;55:113–118.

38. Kampus P, Muda P, Kals J, Ristimae T, Fischer K, Teesalu R et al. The relationship between inflammation and arterial stiffness in patients with essential hypertension. Int J Cardiol. 2006;112:46–51.

39. Assadi F. C-reactive protein and incident left ventricular hypertrophy in essential hypertension. Pediatr Cardiol. 2007;28:280–285.

40. Noronha JAF, Medeiros CCM, Cardoso AdS, Gonzaga NC, Ramos AT, Ramos ALC. C-reactive protein and its relation to high blood pressure in overweight or obese children and adolescents. Rev Paul Pediatr. 2013;31(3): 331–337.

41. Makni E, Moalla W, Benezzeddine-Boussaidi L, Lac G, Tabka Z, Elloumi M. Correlation of resistin with inflammatory and cardiometabolic markers in obese adolescents with and without metabolic syndrome. Obes Facts. 2013;6(4):393–404.

42. Howe LD, Chaturvedi N, Lawlor DA, Ferreira DL, Fraser A, Davey Smith G et al. Rapid increases in infant

adiposity and overweight/obesity in childhood are associated with higher central and brachial blood pressure in early adulthood. J Hypertens. 2014;32(9):1789–1796.

43. Filler G, Rayar MS, da Silva O, Buffo I, Pepelassis D, Sharma AP. Should prevention of chronic kidney disease start before pregnancy? Int. Urol. Nephrol. 2008;40:483–488.

44. Clarke WR, Woolson RF, Lauer RM. Changes in ponderosity and blood pressure in childhood: the Muscatine Study. Am J Epidemiol. 1986;124(2):195–206.

45. Voors AW, Webber LS, Frerichs RR, Berenson GS. Body height and body mass as determinants of basal blood pressure in children — The Bogalusa Heart Study. Am J Epidemiol. 1977;106(2):101–108.

46. Aristimuño GG, Foster TA, Voors AW, Srinivasan SR, Berenson GS. Influence of persistent obesity in children on cardiovascular risk factors: the Bogalusa Heart Study. Circulation. 1984;69(5):895–904.

47. Jiang X, Srinivasan SR, Urbina E, Berenson GS. Hyperdynamic circulation and cardiovascular risk in children and adolescents. The Bogalusa Heart Study. Circulation. 1995;91(4):1101–1106.

48. Madrevica I, Ligere R, Krikis J. Determinant factors of arterial hypertension in school-age boys in Latvia. Endocrine Abstracts. 2002;4: DP9.

49. Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. J Am Med Assoc. 2004;291(17):2107–2113.

50. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350(23):2362–2374.

51. Falkner B, Gidding SS, Ramirez-Garnica G, Wiltrout SA, West D, Rappaport EB. The relationship of body mass index and blood pressure in primary care pediatric patients. J Pediatr. 2006;148(2):195–200.

52. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. Pediatrics. 2004;113(3):475–481.

53. Lo JC, Chandra M, Sinaiko A, Daniels SR, Prineas RJ, Maring BInt J et al. Severe obesity in children: prevalence, persistence and relation to hypertension. Pediatr Endocrinol. 2014;1:3.

54. Kim YK, Kim HU, Song JY. Ambulatory blood pressure monitoring and blood pressure load in obese children. Korean Circ J. 2009;39(11):482–487.

55. Tekın N, Ersoy B, Coskun S, Tekın G, Polat M. Ambulatory blood pressure parameters in office normotensive obese and non-obese children: relationship with insulin resistance and atherosclerotic markers. Med Princ Pract. 2014;23(2):154–159.

56. Obraztsova GI, Gurkina EY. Arterial hypertension in children with obesity. Translational Medicine. 2012;1(12):32–37. [in Russian]

57. Ben-Dov IZ, Bursztyn M. Ambulatory blood pressure monitoring in childhood and adult obesity. Curr Hypertens Rep. 2009;11(2):133–142.

58. Bekezin VV, Kozlova LV, Kozlova IS, Igolkina MV. Peculiarities cardiovascular syndrome in children and adolescents with obesity depending on level of insulin resistance. Cardiology. 2008;3:69–74. [in Russian]

59. Aleksandrov AA. High blood pressure in childhood and adolescence. Russian medical journal. 1997;9:59–65. [in Russian]

60. Avtandilov AG. Arterial hypertension in adolescent males. Moscow, Russian academy of postgraduate education. 1997. [in Russian]

61. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Guerrieri M et al. Altered circadian blood pressure profile and prognosis. Blood Press. Monit. 1997;2:347–452.

62. Lanfranchi P, Somers VK. Obstructive sleep apnea and vascular disease. Respir Res. 2001;2:315–319.

63. Verhulst SL, van Gaal L, de Backer W, Desager K. The prevalence, anatomical correlates and treatment of sleep-disordered breathing in obese children and adolescents. Sleep Medicine Reviews. 2008;12(5):339–346.

64. Marcus L, Curtis S, Koerner CB, Joffe A, Serwint JR, Loughlin GM. Evaluation of pulmonary function and polysomnography in obese children and adolescents. Pediatr Pulmonol. 1996;21(3):176–183.

65. Silvestri JM, Weese-Mayer DE, Bass MT, Kenny AS, Hauptman SA, Pearsall SM. Polysomnography in obese children with a history of sleep-associated breathing disorders. Pediatric Pulmonology. 1993;16(2):124–129.

66. Leung L, Ng D, Lau M, Kwok K, Chow P, Cheung J. Twenty-four-hour ambulatory BP in snoring children with obstructive sleep apnea syndrome. Chest. 2006;130(4):1009–1017.

67. Laurer M, Anderson K, Kannel W, Levy D. The impact of obesity on left ventricle mass and geometry: the Framingham Heart Study. J Am Med Assoc. 1991;266:231–236.

68. Levy D, Murabito JM, Anderson KM. Echocardiographic left ventricular hypertrophy — clinical characteristics — the Framinghan Heart Study. Clin Exp Hypertens. 1992(14):85–97.

69. Vasan RS. Cardiac function and obesity. Heart. 2003;89:1127–1129.

70. Daniels SR, Kimball TR, Morrison JA, Khoury P, Witt S, Meyer RA. Effect of lean body mass, fat mass, blood pressure, and sexual maturation on left ventricular mass in children and adolescents. Statistical, biological, and clinical significance. Circulation. 1995;92(11):3249–3254.

71. Kibar AE, Pac FA, Ballı S, Oflaz MB, Ece I, Bas VN et al. Early subclinical left-ventricular dysfunction in obese nonhypertensive children: a tissue Doppler imaging study. Pediatr Cardiol. 2013;34(6):1482–1490.

72. Ting Fei Ho. Cardiovascular risks associated with obesity in children and adolescents. Ann Acad Med Singapore. 2009;3 (1):48–49.

73. Di Salvo G, Pacileo G, Del Giudice EM, Natale F, Limongelli G, Verrengia M et al. Abnormal myocardial deformation properties in obese, non-hypertensive children: an ambulatory blood pressure monitoring, standard echocardiographic, and strain rate imaging study. Eur Heart J. 2006;27:2689–2695.

74. Villa MP, Ianniello F, Tocci G, Evangelisti M, Miano S, Ferrucci A et al. Early cardiac abnormalities and increased

C-reactive protein levels in a cohort of children with sleep disordered breathing. Sleep Breath. 2012;16(1):101–110.

75. Attia G, Ahmad MA, Saleh AB, Elsharkawy A. Impact of obstructive sleep apnea on global myocardial performance in children assessed by tissue Doppler imaging. Pediatr Cardiol. 2010;31(7):1025–1036.

76. Hedvall Kallerman P, Hagman E, Edstedt Bonamy AK, Zemack H, Marcus C, Norman M et al. Obese children without comorbidities have impaired microvascular endothelial function. Acta Paediatr. 2014;103(4):411–417.

77. Joo Turoni C, Maracyn RO, Felipe V, Bruno ME, Negrete A, Salas N et al. Arterial stiffness and endothelial function in obese children and adolescents and its relationship with cardiovascular risk factors. Horm Res Paediatr. 2013;80(4):281–286.

78. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr. 2009;22(6):709–714.

79. Daniels SR, Meyer RA, Liang YC, Bove KE. Echocardiographically determined left ventricular mass index in normal children, adolescents and young adults. J Am Coll Cardiol. 1988;12(3):703–708.

80. Tudor-Locke C, Craig C, Beets M, Belton S, Cardon G, Duncan S et al. How many steps/day are enough? For children and adolescents. IJBNPA. 2011;8:78.

81. National guidelines for diagnosis, treatment and prevention of hypertension in children and adolescents (second revision). Review of 2009. Cardiovascular therapy and prevention. 2009;8(4). [in Russian]

82. Farpour-Lambert NJ, Aggoun Y, Marchand LM, Martin XE, Herrmann FR, Beghetti M. Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. J Am Coll Cardiol. 2009;54(25):2396–2406.

83. Maggio AB, Aggoun Y, Martin XE, Marchand LM, Beghetti M, Farpour-Lambert NJ. Long-term follow-up of cardiovascular risk factors after exercise training in obese children. J Pediatr Obes. 2011;6(2–2): e603-e610.

84. Hopkins ND, Stratton G, Tinken TM, McWhannell N, Ridges ND, Graves LE et al. Relationships between measures of fitness, physical activity, body composition and vascular function in children. Atherosclerosis. 2009;204(1):244–249.

85. Meyer AA, Kundt G, Lenschow U, Schuff-Werner P, Kienast W. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. J Am Coll Cardiol. 2006;48(9):1865–1870.

86. Hill JM, Zalos G, Halcox JP, Schenke WH, Waclawiw MA, Quyyumi AA et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med. 2003;348(7):593–600.

87. Park JH, Miyashita M, Kwon YC, Park HT, Kim EH, Park JK et al. A 12-week after-school physical activity programme improves endothelial cell function in overweight and obese children: a randomised controlled study. BMC Pediatr. 2012;12:111.

88. Barnes VA, Orme-Johnson DW. Clinical and Preclinical Applications of the Transcendental Meditation Program in the Prevention and Treatment of Essential Hypertension and Cardiovascular Disease in Youth and Adults. Curr Hypertens Rev. 2006;2(3):207–218.

89. Trushkina IV, Fillipov GP, Leontiev IV. Forecasting the development of the metabolic syndrome in adolescence. Pediatrics. 2010:33–36. [in Russian]

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