THE NEW ARMENIAN MEDICAL JOURNAL
Vol.9 (2015), No 3, p.32-38

CARDIOVASCULAR DISORDERS OF METABOLICALLY HEALTHY OBESE ADOLESCENTS

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Received 3/18/2015; accepted for printing 08/22/2015

Abstract

The theory of "metabolically healthy obesity" has become very popular among researchers across the world. Meanwhile, the information about cardiovascular condition of metabolically healthy obese children is rather scant.

The aim of the present study is to improve the knowledge of cardiovascular condition of metabolically healthy obese children compared with those who are lean and healthy and suffer from metabolic syndrome.

Two hundred and eight obese adolescents, grouped as metabolically healthy and metabolically unhealthy, were examined with an analysis of body composition, metabolic parameters, evaluation of left ventricular geometry and function, 24-hours blood pressure monitoring, and carotid intima-media thickness.

The results have shown 69% could be considered as metabolically healthy by the International Diabetes Federation criteria for metabolic syndrome evaluation. Deterioration of cardiovascular parameters was determined in both metabolically healthy and metabolically unhealthy subjects. Eccentric left ventricular hypertrophy with a diastolic dysfunction together with systolic hypertension and thickening of carotid vessels were identified. Systolic-diastolic dysfunction was identified in 22% of metabolically healthy obese and in 54.8% of metabolically unhealthy obese. There was no isolated systolic dysfunction in any child.

It seems unlikely to identify a healthy cardiovascular profile in metabolically healthy obese children. Rather, it should be identified as gradual progression of disorders before detrimental changes. Cardiac imaging and arterial blood pressure monitoring are necessary for the routine examination of all obese kids. It appears the new approaches with a more sensitive cut-offs for metabolic parameters are necessary for identifying metabolic health and making a cardiovascular risk prognosis.

Keywords: *metabolic syndrome, metabolically healthy obese children, myocardial remodeling, myocardial dysfunction, hypertension.*

Introduction

Adiposity is directly associated with cardiovascular risk. The Framingham Heart Study for adults and the Bogalusa Heart Study for pediatric population became the most serious and prolonged trials in this field. However, very little is known regarding the development of cardiometabolic risk in obese children, as the risk stratification demands the presence of cardiovascular events, whose incidence in pediatric practice is very low [*Friedemann C et al., 2012*].

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The theory of "metabolically healthy obesity" (MHO) has become very popular among researchers across the world. Logically, the idea of identification of metabolically healthy subjects outs from the metabolic syndrome (MS) concept – to identify children and adolescents at increased risk of developing type 2 diabetes and cardiovascular disease. Thus, MHO refers to healthy overweight and obese subjects who have normal metabolic features despite increased adiposity [*Waxman A, 2004; Hill J, Wyatt H, 2013; Kramer C et al., 2013*]. It was demonstrated that in contrast to normal weight, metabolically healthy obese people show increased heart failure risk in a 6-year follow-up study [*Voulgari C et al., 2011*]. Meanwhile, some scientists deny obesity as a benign condition and believe obese patients at risk even their metabolic profile is normal [*Kramer C et al., 2013; Ashraf M, 2014; Cho J et al., 2014*].

Meta-analysis of cohort studies shows the different criteria used for the identification leads to misunderstanding the problem and misadjusting data from different scientists [*Roberson L et al., 2014*]. And the first problem is a great difference in reported prevalence of MHO. According to some reports prevalence of MHO could range between 3.3 and 32.1% in men and between 11.4 and 43.3% in women [*Velho S et al., 2010; Primeau V et al., 2011*]. Unfortunately information about the cardiovascular condition of metabolically healthy obese children is rather scant as well as the prevalence of the condition.

The aim of the present study is to improve the knowledge of cardiovascular condition of metabolically healthy obese children compared with those who are lean and healthy and suffer from metabolic syndrome.

MATERIALS AND METHODS

Two hundred and eight obese adolescents (Caucasian) aged 10 to 17 were examined in the Endocrine Department of Kharkiv Regional Children Hospital. The patients were classified into 2 groups: metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) according to the pediatric International Diabetes Federation criteria for metabolic syndrome evaluation [*IDF, 2007*]. It should be noted that in accordance with IDF recommendations 5 critical components of the metabolic syndrome can be emphasized: abdominal obesity, triglycerides level, high-density lipoproteins level, arterial blood pressure, and glycemia. The metabolic syndrome is diagnosed in the presence of 1 to 5 of the abovementioned components, i.e.:

"0" – none of the components is present (does not exceed recommended threshold)

"1" – 1 component is present (abdominal obesity)

"2" – either of 2 components in any combinations (e.g. abdominal obesity + dysglycemia or abdominal obesity + increased high-density lipoproteins level)

"3" and "4" – likewise

"5" – all components exceed the recommended threshold

Anthropometric measurements were performed by using standardized devices and included measurements of height, weight, skin fold, calculated body mass index, body composition [*Reilly J et al., 1995*] and fat predisposition by waist to height ratio [*Barclay L, Lie D, 2010*].

The laboratory assessment of metabolic profile included fasting glucose and insulin with HOMA-IR calculation [*Matthews D, 1985*], oral glucose tolerance test and fasting lipids level: total cholesterol, high density lipoproteins, low density lipoproteins, triglycerides, and free fatty acids.

Left ventricular geometry was assessed by P. Khoury et al (2009) after evaluation of myocardial mass, left ventricular mass index, interventricular septum thickness, relative wall thickness, end-systolic volume, end-diastolic volume. LV function described according to EAE/ASE Recommendations [*Nagueh S et al., 2009*].

Office blood pressure results were interpreted by "The Fourth Report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents". Hypertension was defined as systolic blood pressure or diastolic blood pressure greater than the 95^{th} percentile for age and gender [*National High Blood Pressure Education Program, 2004*], 24-hours blood pressure monitoring results were interpreted by E. Lurbe et al (2004).

Complex intima-media thickness assessed by using Toshiba/Nemio XG/istyle (Japan) and interpreted by [*Dawson J et al., 2009*].

The written informed consent was obtained from the patients and their parents.

The results were analyzed using StatSoft Statistica 10. Quantitative variables were described as means ± SD, qualitative variables were described as percentages. Receiver operating characteristics analysis was employed to calculate the area under the glycemic curve. Differences between groups were established by ANOVA, Mann-Whitney U test. Reported P-values are two-tailed and P-values <0.05 were considered to be statistically significant.

Results

Examination of 208 obese children has demonstrated that only 31% met diagnostic criteria for metabolic syndrome. Thus, abdominal fat predisposition was identified in 86.06±4.80%, dysglycemia (except hypoglycemia) in 9.89±4.14%, dyslipidemia in 37.21±6.70 %, hypertension in 53.45±6.92% of them. The total number of components of the MS decomposed is as follows: "0" in 9.13±3.96%, "1" in 40.87±6.82%, "2" in 21.15±5.65%, "3" in 12.06±4.33%, "4" in 13.98±4.66%, and "5" in 4.81±2.97%. Therefore, about 69% of the obese children under study should be considered as MHO according to the pediatric International Diabetes Federation criteria for the metabolic syndrome evaluation.

Grouping of all obese children into metabolically healthy obese, metabolically unhealthy obese and comparison of relevant data with lean healthy group shows an equal distribution by gender and age (see the table).

Body mass index was greater in MUO than in MHO (p=0.019) due to fat body mass index (p=0.02). The same time no statistical difference in degree of abdominal fat predisposition by the waist to height ratio (p=0.071).

Left ventricular mass index is the best parameter for the evaluation myocardial hypertrophy as it is a relative parameter adjusted to body composition which is important for overweight patients. It was determined that left ventricular mass index was increased in all obese subjects: lean healthy vs. MHO and MUO (p=0.013; 0.002), but without significant difference in MHO vs. MUO (p=0.469).

Detailed analysis show the myocardial mass, relative wall thickness, left ventricular end-systolic and end-diastolic volumes were increased in all obese kids without any statistical difference between MHO and MUO. At the same time interventricular septum thickness and posterior wall thickness were greater in MUO.

Cardiac function assessment demonstrates deterioration of diastolic function in 31.7 % of MHO and in 46.7% of MUO (p=0.04). Systolic-diastolic dysfunction was identified in 22% of MHO and in 54.8 % of MUO (p<0.001). There was no isolated systolic dysfunction in any child. The same time significant differences have been detected in our patients. Both early filling (E) and late diastolic filling (A) flow velocity were decreased in obese vs. lean healthy. E/A ratio acceleration gradually increases due to low A, reaching a statistical difference between MHO and MUO. Deceleration time of early filling velocity and isovolumetric relaxation time are also lower in obese than in control as well as in MUO vs. MHO.

Thus, metabolically healthy obesity demonstrates myocardial eccentric hypertrophy with a normal systolic function and impaired diastolic one despite normal metabolic profile. Peculiarities of the left ventricular function in MUO are due to a more significant impairment of myocardium relaxation. Thus, deterioration of the cardiac structure and function is more significant in MUO.

According to the results of 24-hours blood pressure monitoring, the mean systolic blood pressure in obese is higher than in lean children (p<0.001), and greater in MUO vs. MHO (p=0.014). Simultaneously blood pressure in MHO looks abnormal as the above results 120/80 *mmHg* should be considered as prehypertension for the adolescents. Diastolic blood pressure did not reveal any difference in groups. Systolic blood pressure load in MUO is almost 2 times more significant than in MHO (39.57+5.19 vs. 23.89+2.81; p=0.005). Diastolic blood pressure load did not show relevant differences and was not correspondent to the hypertension (12.33+2.81 vs. 8.33+1.69; p>0.005).

All the obese children demonstrated an increased carotid intima-media thickness vs. the lean healthy children (p<0.001) without significant difference in MHO vs. MUO (p=0.199). There is a reason to confirm the currently existing vascular remodeling for both metabolically healthy and unhealthy obese adolescents.

DISCUSSION

There is a lot of evidence to associate obesity with cardiovascular disorders. Cohort survey of 13 year olds with obesity, conducted by Baylor College of Medicine specialists (USA) in 2007, states the fact that cardiovascular changes in adolescents are similar to those in adults with obesity, and stresses the need for further research of gradual and immediate factors, forming disorders [*Lorch S, Sharkey A, 2007*]. Plenty of data demonstrates that obesity impacts the myocardial geometry and function as in adults [*Abel E et al., 2008; Russo C et al., 2011*] and children [*Dhuper S et al., 2011a,b*].

According to the Strong Heart Study results, obesity plays a key role in cardiovascular disability of adults [*Wang W et al., 2006*]. Myocardial hypertrophy, left ventricular remodeling together with hypertension are also typical for obese chil-

TABLE.

Comparative results of examination metabolically healthy and unhealthy children

Parameters	Lean healthy n=23		Obese adolescents: metabolically healthy, n=145		Obese adolescents: metabolically unhealthy, n=62		p_1	p_2	p_3
	Mean	SD	Mean	SD	Mean	SD			
Basic parameters									
Age	13.78	2.63	14.072	2.928	13.508	3.194	0.656	0.711	0.219
Gender, % of females	44.4		37.2		30.64		0.477	0.228	0.392
Body mass index	18.293	2.778	30.829	5.497	32.825	5.751	<0.001	<0.001	0.019
Lean body mass index	14.347	1.565	17.620	2.474	18.344	2.777	<0.001	<0.001	0.124
Fat body mass index	6.094	1.436	13.036	2.873	14.269	2.827	<0.001	<0.001	0.020
Waist / height	0.407	0.039	0.589	0.089	0.598	0.137	<0.001	<0.001	0.071
Metabolic parameters									
Total cholesterol, *µm/l*	3.284	1.037	4.267	0.747	4.630	0.81	<0.001	<0.001	0.003
Triglycerides , *µm/l*	0.668	0.256	1.166	0.264	1.594	0.57	<0.001	<0.001	<0.001
Free fatty acids, *µm/l*	0.350	0.127	0.422	0.180	0.506	0.19	0.07	0.004	0.002
High density lipoproteins, *µm/l*	1.419	0.349	1.200	0.229	1.060	0.14	<0.001	<0.001	<0.001
Fasting glucose, *µm/l*	3.530	0.673	4.608	1.173	4.698	0.79	<0.001	<0.001	0.583
Fasting insulin, *IE/ml*	10.730	3.861	24.062	11.671	25.545	11.81	<0.001	<0.001	0.431
Homeostasis model assessment-estimated insulin resistance	1.923	0.908	4.954	2.803	5.356	2.578	<0.001	<0.001	0.364
Cardiac parameters									
Myocardial mass	137.83	13.11	191.86	69.42	193.06	52.35	0.003	0.003	0.903
Left ventricular mass index, g/m^2	33.51	4.64	44.486	12.940	46.473	12.32	<0.001	<0.001	0.469
Left ventricular posterior wall thickness, *mm*	7.23	0.04	11.74	2.68	12.57	2.71	<0.001	<0.001	0.030
Left ventricle end diastolic volume, *ml*	102.36	10.14	122.10	22.76	126.47	27.98	<0.001	<0.001	0.229
Left ventricle end systolic volume *ml*	38.14	5.18	47.58	18.89	50.43	20.29	0.011	<0.001	0.319
Interventricular septum thickness, *mm*	7.28	0.23	11.14	1.63	11.79	2.08	<0.001	<0.001	0.017
Relative wall thickness	0.33	0.02	0.35	0.05	0.36	0.03	0.042	<0.001	0.144
Cardiac index, *ml/min/m^2*	2.54	0.52	2.78	0.68	2.87	0.98	0.08	0.129	0.448
Ejection fraction. *%*	63.5	6.58	62.29	7.50	60.88	9.02	0.175	0.434	0.243
A wave, *m/s*	0.46	0.07	0.38	0.08	0.35	0.05	<0.001	<0.001	0.006
E wave, *m/s*	0.94	0.22	0.74	0.27	0.75	0.25	<0.001	<0.001	0.722
E/A ratio	1.3	0.43	2.04	0.66	2.25	0.73	<0.001	<0.001	0.043
Deceleration time, *s*	0.142	0.03	0.120	0.033	0.114	0.027	<0.001	<0.001	<0.001
Isovolumetric relaxation time, *s*	0.112	0.04	0.092	0.06	0.073	0.05	0.011	<0.001	0.025
Vascular parameters									
Mean systolic blood pressure, *mmHg*	116.348	8.205	128.690	10.889	134.303	11.232	<0.001	<0.001	0.014
Mean diastolic blood pressure, *mmHg*	73.913	7.273	74.321	8.232	77.545	7.567	0.829	0.007	0.054
Systolic blood pressure load, *%*	13.79	7.25	23.89	33.83	39.57	40.86	0.151	0.003	0.005
Diastolic blood pressure load, *%*	3.06	6.21	8.33	20.35	12.33	22.12	0.224	0.053	0.208
Complex intima-media thickness, *mm*	0.396	0.048	0.606	0.112	0.642	0.110	0.000	0.000	0.199

NOTES: p_1 - Lean healthy vs metabolically healthy obese, p_2 - Lean healthy vs metabolically unhealthy obese, p_3 - metabolically healthy obese vs metabolically unhealthy obese.

dren [*Hanevold C et al., 2005*]. Cardiac changes in obese are based on two major pathogenic factors: hemodynamic and metabolic [*Rompis J, Kaunang E, 2010; Ashrafian H et al., 2011*]

Our data suggests that all obese children have some kind of myocardial hypertrophy which could be described as eccentric hypertrophy. It absolutely correspondent to mentioned above reports. On addition to this we revealed an interventricular septum hypertrophy, which also described by scientists from Slovakia [*Schustretova I et al., 2013*]. Myocardial mass, relative wall thickness, left ventricular end-systolic and end-diastolic volumes were increased in all obese kids without any statistical difference between MHO and MUO. At the same time, interventricular septum thickness and posterior wall thickness were greater in MUO.

Impairment of the cardiac function in obese patients is mainly associated with reduced left ventricular systolic function. However, quite a high proportion (35-50%) of patients with circulatory failure demonstrated breach of myocardial relaxation with an intact systolic function [*Kuznetsova T et al., 2009*]. Due to this, the fact requiring attention is that isolated systolic dysfunction was not observed in the examined patients, and the systolic and diastolic one was detected in 22% of MHO and 54.8% of MUO.

In the general population the presence of diastolic dysfunction directly correlated with age, body mass index, heart rate, creatinine level, insulin sensitivity [*Leite-Moreira A, 2006*]. Left ventricular end-diastolic properties are determined by external and internal factors. The external include limited mobility due to pathology of the pericardium and interventricular relationships, while the internal ones include myocardial stiffness, tone, and geometry type [*Alpert M, 2001*]. That is why the cardiac remodeling attracts attention to the diastolic function in obese children. However, there is a lack of pediatric studies in this field [*Mehta S et al., 2004; Schustretova I et al., 2013*]. The last of them reports of decreased E/A ratio at septum due to increased peak velocity of late diastolic filling (A) without changes in peak velocity of early diastolic filling (E). In vast majority of our patient pseudonormal filling was considered with increased E/A ratio. We can suppose the different degree of problem in groups of patients (from compensatory supernormal filling to pseudonormal one), which could be also associated with a degree of hypertension in our group that is greater than reported.

Epidemiological study that included 47,000 American children showed the dependence of blood pressure on the body composition [*Rosner B et al., 2000*]. Probability of diagnosing systolic hypertension in obese schoolchildren is 3 times higher versus their lean peers [*Sorof J et al., 2002*]. That is why the obtained results of 24-hours blood pressure monitoring just confirm the previous data and specifies the different degree of systolic hypertension in MHO vs MUO. The resent data shows the strong association between systolic blood pressure level and load with left ventricular mass index in obese children [*Bostanci B et al., 2012; Sharma A et al., 2013*] that contributes to our findings.

There is a lack of relevant information concerning to the cardiac structure and function in metabolically healthy obese children. That is why it is quite difficult to compare our data with previous reports. It seems that both MHO and MUO are at the risk of cardiovascular events. Meanwhile, 31% of them met the criteria for the MS diagnosis, which may indicate underdiagnosis of risk when using these criteria. Similar idea comes from study results of Litwin M. et al (2007), who found moderate left-ventricular hypertrophy in 40.7% and severe one in 12.5% of obese kids with greater body mass index, waist to height ratio, carotid intima-media thickness and greater number of metabolic syndrome components. At the same time, just a small number of obese children demonstrates complete cluster of MS. Even among genetically predisposed Mexican-Hispanic obese children, high triglycerides were detected in 85%, low high density lipoproteins in 60%, hypertension in 35%, and hyperglycemia in 5% of them [*Evia-Viscarra M et al., 2013*].

Thus, the rate of myocardial hypertrophy and dysfunction in obese children is greater than overall rate of metabolic abnormalities. It calls the theory of healthy obesity into question, which is also based upon various studies and our own data. Hence, left ventricular mass index should be measured routinely together with a left ventricular systolic and diastolic function and 24-h blood pressure monitoring be done for adequate risk stratifi-

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cation and prognosis of cardiovascular events in all obese children.

Conclusion

Sixty nine percent of obese adolescents could be identified as metabolically healthy in accordance with the International Diabetes Federation criteria. Meanwhile, all obese children demonstrate deterioration of cardiovascular parameters and metabolically healthy obese beside them despite normal metabolic profile. These cardiovascular disorders include eccentric left ventricular hypertrophy with a diastolic dysfunction together with systolic hypertension, and thickening of carotid vessels. Therefore it seems unlikely to define completely healthy cardiovascular profile in metabolically healthy obese children. Rather, it should be identified as gradual progression of disorders before detrimental changes. Cardiac imaging together with ambulatory blood pressure monitoring is necessary for the routine examination of all obese children. It appears some new approaches with a more sensitive cut-offs for metabolic parameters are necessary for identifying metabolically healthy obesity for the exact cardiovascular risk prognosis

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