

Original research article

RISK RELATED CARDIOVASCULAR CHANGES IN METABOLICALLY HEALTHY OBESE ADOLESCENTS

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Abstract:

Background: Pediatric obesity reflects a real crisis for public health as associated with cardiovascular risk in subjects with developed metabolic syndrome. Simultaneously the information concerning risk related cardiovascular changes in metabolically healthy obese adolescents is pretty insufficient.

Methods: 208 obese adolescents were grouped as metabolically healthy and metabolically unhealthy by IDF criteria for pediatric metabolic syndrome. We analyzed the basic metabolic parameters, left ventricular geometry and function, 24-hours BP monitoring and carotid intima-media thickness. Control group consisted of 23 lean healthy subjects.

Results: 69% of obese adolescents could be considered as metabolically healthy by pediatric IDF criteria. BMI in metabolically unhealthy was greater vs. metabolically healthy ($p=0,019$) as well as dyslipidemia and dysglycemia. Cardiovascular parameters were deteriorated in all obese vs. lean healthy (myocardial hypertrophy and dysfunction, thickening of carotid vessels and systolic hypertension). It established low sensitivity ($Se = 0,28$) and low negative predictive value ($NPV=0,29$) of metabolic syndrome criteria to screen obesity associated cardiovascular problems.

Conclusion: Prognostic capability of pediatric metabolic syndrome criteria is pretty low due to its sensitivity. Therefore obese adolescents not met diagnostic level for metabolic syndrome by IDF criteria could be falsely excluded from the cardiovascular risk group. Thus, it's not possible to assert an existence of absolutely healthy metabolic profile in obese and more sensitive markers are necessary for the metabolically healthy obesity identification.

Key words: cardiovascular risk, metabolic syndrome, metabolically healthy obese, adolescents

Introduction:

Pediatric obesity reflects a real crisis for public health [1] as it is associated with an increased occurrence of cardiovascular and metabolic disorders, orthopedic and psychiatric complaints together with a low self-esteem [2]. Compared with lean healthy, obese individuals are at increased risk for adverse long-term outcomes [3, 4] as each kg/m^2 of BMI gained is associated with an 18% increase in the risk of developing hypertension and a 26% increase in risk for the complete cluster of metabolic syndrome [5] and dyslipidemia [6]. Thus, adiposity is associated directly with cardiovascular risk. Simultaneously, the majority of the risk criteria are metabolic with an only exception as blood pressure. However, very little is known regarding the impact of metabolic derangements at cardiovascular risk development in children. This is, probably, due to fact of low paediatric incidence of acute cardiovascular events, which are necessary for the risk stratification [7].

The concept of “metabolically healthy obesity” has become popular recently and is defined as healthy overweight and obese subjects with normal metabolic features despite increased adiposity [8-10]. Thus, it suggested that metabolically healthy obese have a decreased heart failure risk in a 6-year follow-up study in contrast to normal weight subjects [11]. However, others argue that obesity per se is not a benign condition and obese subjects are at risk in spite of normal metabolic profile [12-14].

Obese children and adolescents tend to become an obese adults [15] and have a 16-fold higher risk of becoming severely obese adults with a BMI above 40 kg/m^2 as compared to normal weight adolescents [16]. Logically, some of obese adolescents could be considered as metabolically healthy. Understanding of acute events' risk in them is pretty uncertain due to insufficient data of their cardiovascular profile.

This study is therefore designed to determine the risk related cardiovascular changes in metabolically healthy obese adolescents

Subjects and Methods:

208 obese adolescents (Caucasian) aged 10 to 17 were examined. All subjects were classified into 2 groups: metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) according to the pediatric IDF criteria for metabolic syndrome evaluation [17].

Anthropometric measurements were performed by using standardized devices: Harpenden stadiometer, SECA weight scale. BMI was calculated as body weight (kg) divided by squared standing height (m²). Obesity estimated by WHO cut-offs when BMI was greater than or equal + 2 SD. BMI z-scores used to compare between group means. Abdominal adiposity assessed by waist to height ratio (WHR) [18] and result greater than or equal 0,5 was considered as positive for the central obesity.

The laboratory assessment of metabolic profile included fasting lipids, glucose, insulin and HOMA-IR [19], oral glucose tolerance test (OGTT).

Left ventricular (LV) geometry assessed by P.Khoury et al. [20] and LV function according to EAE/ASE Recommendations [21].

Hypertension was defined as office systolic blood pressure (SBP) or diastolic blood pressure (DBP) greater than the 95th percentile for age and gender by “The Fourth Report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents” [22], ambulatory blood pressure monitoring (ABPM) results were interpreted by E.Lurbe et all. [23].

Carotid intima-media thickness (CIMT) assessed by using Toshiba/Nemio XG/istyle and interpreted by [24].

Written informed consent was obtained from the patients and their parents.

Statistical analysis. The results were analyzed using StatSoft Statistica 10. Quantitative variables were described as means \pm SD, qualitative variables were described as percentages. Differences between groups were established by ANOVA and Mann-Whitney U test. Reported P-values are two-tailed and P-values $<0,05$ were considered to be statistically metabolic syndrome criteria to predict obesity associated cardiovascular problems. Binary classification used for estimation sensitivity (Se), Specificity (Sp), negative predictive value (NPV) and positive predictive value (PPV).

Results.

There were no age and gender differences between groups (**table 1**). BMI was greater in MUO than in MHO in both absolute values ($p = 0,019$) and Z-scores ($p < 0,0001$) with no difference in degree of abdominal adiposity by WHR ($p = 0,744$).

Analysis of basic metabolic parameters shown the fasting total cholesterol (TC), triglycerides (TG) were higher in MUO and HDL level lower respectively. Fasting blood glucose was higher in obese vs. lean ($p < 0,001$ for both), but no difference MHO vs. MUO ($p = 0,583$) as well as fasting insulin level and HOMA-IR ($p = 0,431$; $0,364$, respectively). It was established that 91 % of MHO and 100% of MUO were insulin resistant ($p = 0,014$). OGTT revealed Type 2 Diabetes in 4,8 % of MUO children, impaired fasting glucose in 6,89 % MHO and in 19,35 % MUO ($p = 0,008$), impaired glucose tolerance in 1,38% MHO and in 11,29 MUO ($p < 0,001$).

Table 1. Basic, metabolic and cardiovascular parameters of metabolically healthy obese adolescents vs. metabolically unhealthy and lean ones

Parameters	Lean healthy, n = 23		Obese				LH vs MHO, p	LH vs MUO, p	MHO vs MUO, p
			MHO, n = 145		MUO, n = 62				
	Mean	SD	Mean	SD	Mean	SD			
Basic parameters									
Age, years	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
BMI, Z-score	0,111	0,983	2,65	0,738	3,11	0,898	<0,001	<0,001	<0,001
BMI, kg/m ²	18,29	2,778	30,829	5,497	32,825	5,751	<0,001	<0,001	0,019
	3								
WHR	0,407	0,039	0,589	0,089	0,598	0,137	<0,001	<0,001	0,744
Metabolic parameters									
TC, mmol/l	3,284	1,037	4,267	0,747	4,630	0,809	<0,001	<0,001	0,003
TG, mmol/l	0,668	0,256	1,166	0,264	1,594	0,573	<0,001	<0,001	<0,001
HDL, mmol/l	1,419	0,349	1,200	0,229	1,060	0,144	<0,001	<0,001	<0,001
Glucose fasting, mmol/l	3,530	0,673	4,608	1,173	4,698	0,786	<0,001	<0,001	0,583
Insulin fasting, pmol/l	74,51	26,80	167,11	81,04	177,41	76,11	<0,001	<0,001	0,431
	2	7	1	8	0	1			
HOMA-IR	1,923	0,908	4,954	2,803	5,356	2,578	<0,001	<0,001	0,364
Cardiovascular parameters									
SBP, mmHg	116,3	8,205	128,69	10,88	134,30	11,23	<0,001	<0,001	0,014
	5			9	3	2			
DBP, mmHg	73,91	7,273	74,321	8,232	77,545	7,567	0,829	0,007	0,054
	3								
SBP load (24h), %	13,79	7,25	23,89	33,83	39,57	40,86	0,151	0,003	0,005
DBP load (24h), %	3,06	6,21	8,33	20,35	12,33	22,12	0,224	0,053	0,208
CIMT, mm	0,396	0,048	0,606	0,112	0,642	0,110	0,000	0,000	0,199
LVMI, g/m ²	37,51	4,64	44,486	12,94	46,473	12,32	0,013	0,002	0,469
				0		3			

Normal BP was registered in $25,00 \pm 8,66\%$ of MHO and $5,13 \pm 5,69\%$ MUO ($p=0,01$). 1-st degree of hypertension was predominant in MHO ($p=0,04$) and by contrast the 2-nd degree of hypertension was common for MUO ($p<0,001$).

Analysis ABPM results shown the mean SBP in obese higher than in lean ($p<0,001$) as well as in MUO is greater vs. MHO ($p=0,014$). Simultaneously average BP in MHO looks abnormal as the results above 120/80 mmHg should be considered as prehypertension for the adolescents [22]. DPB didn't reveal any difference in groups. SBP load in MUO almost 2 times more significant than in MHO ($39,57 \pm 5,19$ vs. $23,89 \pm 2,81$; $p=0,005$). DBP level did not correspond to the hypertension and its' load didn't show differences in groups ($12,33 \pm 2,81$ vs. $8,33 \pm 1,69$; $p>0,005$).

All obese children demonstrated an increased CIMT vs lean healthy subjects ($p<0,001$) with no difference between MHO and MUO ($p=0,199$).

Left ventricular mass indexed (LVMI) is a relative parameter adjusted to body composition for the evaluation of myocardial hypertrophy. It was established that LVMI was increased in all obese subjects: LH vs. MHO and MUO ($p=0,013$; $0,002$), with no difference between MHO and MUO ($p=0,469$).

Cardiac function assessment demonstrates the number of patients with an isolated diastolic dysfunction is greater between MUO (46,7 %) than MHO (31,7 %) ($p = 0,04$). Systolic-diastolic dysfunction was identified in 22 % of MHO and in 54,8 % of MUO ($p < 0,001$). The same time there was no patients with an isolated systolic dysfunction in groups. Thus, both MHO and MHO had myocardial hypertrophy with myocardial dysfunction, increased carotid intima-media thickness and were hypertensive. The only difference is degree of the named derangements.

As soon the majority of both groups were positive for cardiovascular risk markers, we determined the screened capacity of metabolic syndrome criteria

for obesity associated cardiovascular problems. Obese patients who had at the same time hypertension, myocardial hypertrophy, carotid intima-media thickening were marked as “risky” and stateless - as "not risky". It established the high specificity ($Sp = 0,96$) and low sensitivity ($Se=0,28$) of IDF MS criteria in terms of screening children with obesity related cardiovascular problems. The positive predictive value is really high ($PPV = 0,96$), but negative predictive value is pretty low ($NPV = 0,29$). Total prognostic value is 0,62. Thereby, there is high likelihood of existence of risk associated cardiovascular changes in metabolically healthy (less than 3 metabolic syndrome components) obese adolescents.

Discussion.

The study shows, that 69 % of obese adolescents might be considered as metabolically healthy (less than 3 metabolic syndrome components by IDF recommendation). This number is greater than previously reported for adults, as prevalence of MHO ranges between 3,3 and 32,1% in men and between 11,4 and 43,3% in women [25, 26]. To understand this gap we searched results of cohort studies and realized the different researchers use different criteria for the MHO consideration [27]. Unfortunately relevant information about percentage of metabolically healthy obese children is unavailable.

Comparative analysis of body composition shows the MUO have greater BMI vs. MHO, which corresponds with reported data [28]. The same time, even rapid growth of BMI and early onset of obesity in children were not confirmed as a harmful or protective in terms of cardiovascular risk [29]. DEXA-scan is the golden standard for the body composition measurement and visceral adiposity assessment. Simultaneously waist to height ratio is simple and valid marker for clinical use [18], which predicts adiposity even better than BMI [30]. The recent data suggest the result ≥ 0.55 identified central obesity with a high probability [31]. As soon we didn't reveal any difference in WHR the same degree of

central obesity is highly suspected in groups. As soon as visceral fat positively correlates with increased LVM indexed (LVMI) and preserved LV function [32, 33], the relevant problems could be expected in both MHO and MUO.

Analysis of metabolic parameters shows that lipids and carbs differ in both groups of obese vs. lean healthy subjects. The main peculiarity of MHO vs. MUO metabolic profile are lipid parameters not exceed recommended levels for the metabolic syndrome, but were correspondent to borderline high (low for HDL) according to NCEP for children [34].

There is a current data that 30% of MHO children are insulin resistant [35]. Stepwise deterioration of pancreatic function at glucose load at insulin resistance background is correspondent to previously reported for adults [36].

Hypertension, left ventricular hypertrophy, carotid intima-media thickening are independent predictors of acute cardiovascular events in adults [37, 38]. According to the Strong Heart Study both overweight and obese subjects had greater LV diameter and mass than normal-weight adults [39]. In turn, obese children show increased LVMI and preserved LV function [40]. The Muscatine Offspring Study shown the CIMT is positively correlated with SBP, BMI, and WHR [41]. Our data suggest LV hypertrophy, systolic hypertension and carotid intima-media thickening correspond to reported and complement them in term of greater violation of cardiac and vascular function in MUO. It worth mention that both MHO and MUO have deteriorated cardiovascular parameters.

Some study reports cardiovascular risk in MHO children is 21,5% [42]. Moreover the presence of diastolic dysfunction is considered as a risk factor for cardiovascular events [43, 44] as well as prehypertension [45, 46], which tends to become a hypertension very soon [47]. The last statement confirmed by our data, which revealed the SBP gradually growing from lean to MUO so by the level as by the load.

Consequently, there is no compelling evidence for the completely healthy metabolic profile in MHO children as vast majority of them are insulin resistant with lipid parameters correspondent to borderline high levels by NCEP. Therefore all obese children should be considered as risky as it was shown in Bogalusa Heart Study [48]. Selection of diagnostic criteria for MHO plays an important role for the cardiovascular risk screening [27].

Conclusively obesity associated cardiovascular problems (myocardial hypertrophy and dysfunction, thickening of carotid vessels and systolic hypertension) are present in both metabolically healthy and metabolically unhealthy obese adolescents.

Prognostic capability of pediatric metabolic syndrome criteria is pretty low due to its sensitivity. Therefore obese adolescents not met diagnostic level for metabolic syndrome by IDF criteria could be falsely excluded from the cardiovascular risk group. Thus, from the one hand, it's not possible to assert an existence of absolutely healthy metabolic profile in obese. From the other hand, more sensitive markers are necessary for the metabolically healthy obesity identification.

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