

## **Anthropometric and metabolic parameters to distinguish metabolically healthy obese children from children with metabolic syndrome.**

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### **Abstract**

**Background:** Obesity plays a central role in the Metabolic Syndrome (MS), which is defined as a clustering of cardio-metabolic risk factors, including central obesity, abnormalities in glucose metabolism, hypertension and dyslipidaemia; so, with the increasing of obesity we also witnessed the increase of MS cases. As well as in adults, even in children has been described the metabolically healthy obese that identify all obese subjects without metabolic disorders.

**Objective:** The objective of this study was to evaluate one or more parameters able to distinguish obese children metabolically healthy and those potentially at risk of metabolic and cardio-vascular complications.

**Methods:** We evaluated anthropometric and metabolic parameters in 125 overweight and obese children and adolescents (64 M and 61 F) aged 10-16 years (mean age 12.09) with Body Mass Index >85th percentile. According IDF consensus, we divided our children in three groups: obese with metabolic syndrome (MS), obese with alteration of one metabolic parameter (Metabolic Unhealthy obese or MUO) and obese metabolically healthy (MHO). We performed a statistical analysis by a "post hoc" Fisher's LSD analysis, in order to highlight significant differences between means and Standard Deviations of the parameters analyzed among the three groups.

**Results:** 15 children (12%), were diagnosed as suffering from Metabolic Syndrome; 45 (36%) could be considered metabolically unhealthy obese and 65 children (52%) could be considered metabolically healthy obese. systolic blood pressure, diastolic blood pressure and tryglicerides values was statistically significant between all the three groups faced each other.

**Keywords:** Children obesity, Metabolic syndrome, Metabolic healthy obese.

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### **Introduction**

Childhood obesity is a worldwide epidemic disease, difficult to manage both for therapeutic and preventive level due to its multifactorial nature.

In 2015, World Health Organization (WHO) updated "factsheet" and showed that in 2013, 42 millions of children under five were overweight or obese [1].

In Italy, in 2014, surveillance system "Okkio alla SALUTE" showed nation among the first in Europe for the excess weight with a prevalence of overweight in children of 20,9% and a prevalence of obesity of 9,8%, including severely obese children accounted for 2,2% [2].

More than 60% of obese in pre-puberty remain obese in

adulthood and it is known that obesity in young is closely associated with cardiovascular disease development [3].

Obesity plays a central role in the Metabolic Syndrome (MS), which is defined as a clustering of cardio-metabolic risk factors, including central obesity, abnormalities in glucose metabolism, hypertension and dyslipidaemia [4,5]; so, with the increasing of obesity we also witnessed the increase of MS cases.

However, diagnosis of MS in adulthood is clinically recognized, but it is not yet available a clear definition in pediatric patients: during the last decades there have been many definitions proposed, trying to transpose adulthood definition in childhood [6]. The currently most widely accepted definition is the International Diabetes Federation

(IDF) definition performed for pediatric population in 2007. MS is defined in child from 10 to 16 years by the presence of central obesity (waist circumference  $\geq$  90<sup>th</sup> percentile) plus two of other criteria (triglycerides  $\geq$  150 mg/dl, HDL < 40 mg/dl, blood pressure systolic  $\geq$  130 mm Hg and/or diastolic  $\geq$  85 mm Hg, fasting plasma glucose  $\geq$  100 mg/dl or T2D) [7].

The prevalence of MS in childhood is different, depending on the criteria used [8]: On average is reported a prevalence of 3,3% in the general population, 11,9% in overweight and 29,2% in obese children, with higher rates when using criteria and reference ranges for age [9].

Recently it has been proposed the definition of "healthy obesity": the term has been suggested as a subtype in the classification of obesity and identify all obese subjects without metabolic disorders [10,11]: Prevalence of Metabolically Healthy Obesity (MHO) in adult is reported to be between 10 and 51%, varying with the definition of MHO proposed [12-15]; in childhood we are still few studies about, but is described a prevalence of obesity without metabolic alterations between 21 and 68%, being however not yet defined the criteria used to define the status of "metabolically healthy individual" in this age group [16-18].

In the light of all, it is useful to establish criteria to identify obese children metabolically healthy and those potentially at risk of metabolic and cardio-vascular complications, identifying the anthropometric and/or metabolic parameters predictive of disease.

### **Purpose of the Study**

- 1) To determine in our obese children the prevalence of MS in the age group 10-16 years, according to IDF criteria
- 2) To determine the prevalence of children who, while being overweight, not show any alteration of metabolic parameters of the disease and may be classified as MHO
- 3) To identify the anthropometric or laboratory factors that might predict the onset of Metabolic Syndrome, MS.

### **Materials and Methods**

#### **Subjects**

We collected clinical and laboratory data on 125 overweight and obese children and adolescents (64 M and 61 F) aged 10–16 years (mean age 12.09) with Body Mass Index (BMI) > 85<sup>th</sup> percentile who were consecutively referred to the Pediatric Endocrine and Obese Clinic of San Salvatore Hospital, L'Aquila (Italy), between November 2014 and April 2016 for evaluation of obesity. Exclusion criteria were secondary obesity, syndromes and other illnesses, as well as use of medications known to alter blood pressure, lipid or glucose metabolism.

#### **Anthropometric Measurements**

Subjects were measured wearing light clothing and without shoes.

Weight and body composition were measured with the bioimpedance analyser TANITA BC-418 MA, which measured weight to the nearest 0.1 kg and calculated estimates of truncal and total fat and lean mass.

Standing height was measured with a HOLTAIN stadiometer to the nearest 0,1 cm.

BMI was calculated using the formula  $BMI = kg/m^2$ .

Based on age and sex-specific percentile values for each child, BMI for age was expressed as BMI-SDS using the Cacciari growth charts [19].

Pubertal development stage was evaluated by a pediatric endocrinologist according to Tanner based on breast development and genital size [20].

Waist Circumference (WC) was measured as the minimal circumference measurable on the horizontal plan between the lowest portion of the rib cage and iliac crest, with a tape measure, in a standing position [21].

The values of WC percentile were established according to table provided by IDF consensus definition of the metabolic syndrome in children and adolescents for European population.

Waist-to-height ratio was calculated, too [22].

After the children have rested for five minutes and were in a sitting position, systolic (SBP) and diastolic blood pressure (DBP) measurements were taken, using a mercury gravity manometer and a cuff appropriate body size.

#### **Blood Samples**

After an overnight fast (12 h), venous blood samples were taken from the patients for the measurements of biochemical parameters.

Laboratory data collected included: Fasting Plasma Glucose (FPG) and Insulin (FPI), serum levels of Triglycerides (TG), High-Density Lipoprotein Cholesterol (HDL-C), 25-hydroxyvitamin D (vit. D), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-Glutamyl Transpeptidase (GGT), Thyroid Stimulating Hormone (TSH), FT3 and FT4.

Following the fasting blood sampling, a standard oral glucose tolerance test (OGTT) was performed using 1.75 g/kg (maximum 75 g) glucose. Venous blood samples were obtained at 0, 30, 60, 90, 120 minutes for the determination of plasma glucose and serum insulin levels.

Plasma glucose, insulin, triglycerides, HDL cholesterol, AST, ALT,  $\gamma$ GT, were analyzed with ARCHITECT analyzer (by Abbott); TSH, FT3, FT4 were analyzed using Chemiluminescent Microparticle Immunoassay (ARCHITECT by Abbott); 25-hydroxyvitamin D was measured with Chemiluminescent Microparticle Immunoassay (LIAISON by DiaSorin).

Glucose and insulin levels from the OGTT were used to estimate basal Insulin Resistance (IR) using the

homeostatic model assessment (HOMA-IR), method based on fasting insulin and glucose concentration: fasting blood glucose (mg/dl)  $\times$  fasting insulin (mg/dl)/405.

#### **Definition of Obese Children with Metabolic Syndrome**

MS was defined according to the criteria of the IDF consensus for 10-16 years old children and adolescents [7].

Subjects were classified as having MS when they had WC  $\geq$  90<sup>th</sup> percentile for gender, age and ethnic origin and two or more of the following abnormalities:

- HDL-C < 40 mg/dl;
- TG  $\geq$  150 mg/dl;
- Systolic Blood Pressure (SBP)  $\geq$  130 mm Hg or Diastolic Blood Pressure (DBP)  $\geq$  85 mm Hg;
- FPG  $\geq$  100 mg/dl.

#### **Definition of Metabolically Healthy Obese Children**

We defined MHO, children that did not have the metabolic alterations evaluated for MS MetS. Thus, subjects with all of the following findings were classified as MHO children:

- HDL-C  $\geq$  40 mg/dl;
- TG < 150 mg/dl;
- Systolic Blood Pressure (SBP) < 130 mm Hg or Diastolic Blood Pressure (DBP) < 85 mm Hg;
- FPG < 100 mg/dl.

#### **Definition of Metabolically Unhealthy Obese Children**

We defined Metabolically Unhealthy Obese (MUO) children that had only one or more of the following finding out of the normal range: HDL-C, TG, SBP, DBP, FPG.

#### **Statistics**

All statistical analysis was performed by Statgraphics–Centurion Ver XV statistical package.

Results were presented as percent or mean  $\pm$  Standard Deviation (SD). The difference in the mean of variables between MS group, MHO group and borderline obese group (MUO) were tested by ANOVA. A “post hoc” Fisher's LSD analysis was performed by using the independent “t” test in case of normally distributed continuous variable. Distribution was tested for normality using the Shapiro – Wilk test.

All probability values less than 0.05 were considered statistically significant.

#### **Results**

In our 125 overweight and obese children, 15 (6 M and 9 F) (12%), are diagnosed as suffering from MS according the IDF criteria; 45 (27 M and 18 F) (36%), that present alteration of one metabolic parameter but that not meet all the criteria for diagnosis of MS, can be considered MUO; 65 children (31 M and 34 F) (52%) have no metabolic alterations and can be considered MHO.

In the first group, children with MS, mean of age is 11.97  $\pm$  1.59 years, and mean pubertal status is 2.8  $\pm$  1.42, according Tanner definition; in the second group, MUO children, mean of age is 12.22  $\pm$  1.86 with a pubertal status of 2.57  $\pm$  1.55; the third group, MHO children, has a mean of age of 12.02  $\pm$  1.54 years and a pubertal status of 2.95  $\pm$  1.62: the three groups are demographically homogeneous.

Means and SD of the anthropometric parameters of MS group are: BMI 31.2  $\pm$  4.8, BMI-SDS 2.3  $\pm$  0.5; in the MUO group BMI is 28.9  $\pm$  3.9, BMI-SDS is 2.0  $\pm$  0.4 and in the MHO group BMI is 28.3  $\pm$  3.8, BMI-SDS is 1.9  $\pm$  0.4: we notice that MS group presents obesity levels slightly higher in relation to other two groups (Table 1).

In our sample, all children have a WC  $\geq$  90<sup>th</sup> percentile for gender, age and ethnic origin with a mean of 93.9  $\pm$  8.5 centimetres (cm) for MS group, 88.2  $\pm$  9.1 cm for MUO group and 85.5  $\pm$  8.1 cm for MHO children: we notice how WC shows a directly relation with metabolic alterations; trunk and total fat mass evaluated by bio impedance analyzer show the same trend (Table 1).

Mean values for SBP, DBP, TG, HDL-C, AST, ALT, GGT, FPG, FPI, 2 h plasma glucose, 2 h plasma insulin and vitamin D: all these parameters show a positive trend (negative for HDL-C and vitamin D) from MHO to MS children. In Table 1 are reported means and SD for all these parameters.

Applying a multiple comparison procedure (ANOVA) to determine which means were significantly different between the three analysed groups, we found that the difference of means relatively to the anthropometric parameters (weight, BMI, BMI SDS, WC), body composition parameters (truncal fat mass, total fat mass) and FPI, showed statistical significance between the subjects with MS compared to the others (MUO and MHO) but not between MUO and MHO (Table 2).

The difference of means of ALT and GGT was significant between MHO and other groups but not between MUO and MS (Table 3).

The difference of means of, SBP, DBP and TG values was statistically significant between all the three groups MS, MHO and MUO, faced each other (Table 4).

The parameter "2 h serum insulin" was significant between MS group versus MHO but not versus MUO, and was similar between MUO and MHO (Table 5).

The values of FPG, 2 h plasma glucose from OGTT, 25-OH Vit. D and AST did not show any statistically significant difference between the three groups (Table 6).

#### **Discussion**

The first aim of our study was to determine the prevalence of MS according the IDF criteria in our population of overweight and obese children between 10-16 years: we observe a prevalence of MS of 12%, in agreement with the most part of the literature [9]. Concerning the MHO

**Table 1.** Demographic, anthropometric, clinic and laboratory parameters in MS, MUO and MHO children (mean values and SD)

	<b>MS</b>	<b>MUO</b>	<b>MHO</b>
<b>Age</b>	11.97 ± 1.59	12.22 ± 1.86	12.02 ± 1.54
<b>Puberty</b>	2.8 ± 1.42	2.57 ± 1.55	2.95 ± 1.62
<b>BMI (Kg/m<sup>2</sup>)</b>	31.2 ± 4,8	28.9 ± 3.9	28.3 ± 3.8
<b>BMI-SDS</b>	2.3 ± 0.5	2.0 ± 0.4	1.9 ± 0.4
<b>WC (cm)</b>	93.9 ± 8.5	88.2 ± 9.1	85.5 ± 8.1
<b>Truncal fat mass (Kg)</b>	12.8 ± 3.9	10.5 ± 2.9	10.2 ± 3.1
<b>Total fat mass (Kg)</b>	31.7 ± 10.8	25.2 ± 7.7	23.8 ± 6.9
<b>SBP (mmHg)</b>	128.7 ± 9.7	121.9 ± 9.2	113.3 ± 9.9
<b>DBP (mmHg)</b>	80.3 ± 8.2	75.1 ± 9.2	70.8 ± 6.9
<b>TG (mg/dl)</b>	132.7 ± 61.0	93.6 ± 46.4	69.3 ± 26.9
<b>HDL-C (mg/dl)</b>	34.13 ± 4.1	40.4 ± 17.2	51.4 ± 19.9
<b>AST (UI/l)</b>	24.5 ± 4.0	23.1 ± 7.8	21.8 ± 3.8
<b>ALT (UI/l)</b>	27.7 ± 10.0	26.2 ± 16.5	20.1 ± 7.2
<b>GGT (UI/l)</b>	21.4 ± 6.8	19.0 ± 6.8	16.1 ± 5.9
<b>FPG (mg/dl)</b>	78.8 ± 7.6	77.5 ± 11.1	77.0 ± 9.1
<b>FPI (mg/dl)</b>	22.6 ± 19.0	15.8 ± 7.1	14.3 ± 7.9
<b>2 h plasma glucose (mg/dl)</b>	112.0 ± 14.0	103.3 ± 17.6	104.6 ± 19.0
<b>2 h plasma insulin (mg/dl)</b>	113.0 ± 106.0	95.4 ± 87.4	68.2 ± 51.2
<b>Vitamin D (ng/ml)</b>	18.1 ± 12.0	16.6 ± 8.2	16.6 ± 6.8

**Table 2.** ANOVA and post-hoc Fisher's LSD analysis

	<b>Subjects with MS</b>	<b>Metabolically Unhealthy Obese (MUO)</b>	<b>Metabolically Healthy Obese (MHO)</b>	<b>F-ratio</b>	<b>p-Value</b>
Weight (kg)	75.6 ± 17.0	68.5 ± 14.5	65.5 ± 13.3	4.32	0.0154
BMI (kg/m <sup>2</sup> )	31.2 ± 4.8	28.9 ± 3.9	28.3 ± 3.8	5.17	0.0070
BMI SDS	2.3 ± 0.5	2.0 ± 0.4	1.9 ± 0.4	5,01	0.0081
WC (cm)	93.9 ± 8.5	88.2 ± 9.1	85.5 ± 8.1	6.97	0.0014
Truncal fat mass (kg)	12.8 ± 3.9	10.5 ± 2.9	10.2 ± 3.1	3.89	0.0232
Total fat mass (kg)	31.7 ± 10.8	25.2 ± 7.7	23.8 ± 6.9	6.06	0.0031
FPI (mcU/ml)	22.6 ± 19.0	15.8 ± 7.1	14.3 ± 7.9	5.34	0.0060
MS vs. MUO	p<0.05				
MS vs. MHO	p<0.05				
MUO vs. MHO	ns				

**Table 3.** ANOVA and post-hoc Fisher's LSD analysis

	<b>Subjects with MS</b>	<b>Metabolically Unhealthy Obese (MUO)</b>	<b>Metabolically Healthy Obese (MHO)</b>	<b>F-ratio</b>	<b>p-Value</b>
<b>ALT (UI/l)</b>	27.7 ± 10.0	26.2 ± 16.5	20.1 ± 7.2	4.43	0.0141
<b>GGT (UI/l)</b>	21.4 ± 6.8	19.0 ± 6.8	16.1 ± 5.9	6.55	0.0021
<b>HDL-C (mg/dl)</b>	34.13 ± 4.1	40.4 ± 17.2	51.4 ± 19.9	8.08	0.0005
MS vs. MUO	ns				
MS vs. MHO	p<0.05				
MUO vs. MHO	p<0.05				

children, the prevalence in our population is 52%, at the upper limits than that previously reported in other works [13]; we remember that this prevalence is highly variable, depending the classification used [18].

In order to identify predictive parameters for cardio-

metabolic risk, we have noticed, as yet showed, that anthropometric measurements (weight, BMI, WC) and body composition parameters (truncal fat mass and total fat mass), as well as the values of fasting plasma insulin (FPI), are crucial in identifying MS patients from the others groups, but are not useful to differentiate children MUO

**Table 4.** ANOVA and post-hoc Fisher's LSD analysis

	Subjects with MS	Metabolically Unhealthy Obese (MUO)	Metabolically Healthy Obese (MHO)	F - ratio	
<b>SBP (mm Hg)</b>	128.7 ± 9.7	121.9 ± 9.2	113.3 ± 9.9	18.46	0.0000
<b>DBP (mm Hg)</b>	80.3 ± 8.2	75.1 ± 9.2	70.8 ± 6.9	10.26	0.0001
<b>TG (mg/dl)</b>	132.7 ± 61.0	93.6 ± 46.4	69.3 ± 26.9	14.74	0.0000
MS vs. MUO p<0.05					
MS vs. MHO p<0.05					
MUO vs. MHO p<0.05					

**Table 5.** ANOVA and post-hoc Fisher's LSD analysis

	Subjects with MS	Metabolically Unhealthy Obese (MUO)	Metabolically Healthy Obese (MHO)	F-ratio	p-Value
<b>2 h serum insulin (mg/dl)</b>	113.0 ± 106.0	95.4 ± 87.4	68.2 ± 51.2	3.02	0.0529
MS vs. MUO ns					
MS vs. MHO p<0.05					
MUO vs. MHO ns					

**Table 6.** ANOVA and post-hoc Fisher's LSD analysis

	Subjects with MS	Metabolically Unhealthy Obese (MUO)	Metabolically Healthy Obese (MHO)	F-ratio	p-Value
<b>FPG (mg/dl)</b>	78.8 ± 7.6	77.5 ± 11.1	77.0 ± 9.1	0.13	0.8807
<b>2 h plasma glucose (mg/dl)</b>	112.0 ± 14.0	103.3 ± 17.6	104.6 ± 19.0	1.34	0.2673
<b>25-OH vitamin D (ng/ml)</b>	18.1 ± 12.0	16.6 ± 8.2	16.6 ± 6.8	0.39	0.6825
<b>AST (UI/l)</b>	24.5 ± 4.0	23.1 ± 7.8	21.8 ± 3.8	0.83	0.4382
MS vs. MUO ns					
MS vs. MHO ns					
MUO vs. MHO ns					

from MHO, so they aren't apparently early predictive parameters [16,17,23].

Liver damage indices (ALT and GGT) and HDL-C present statistically significant differences between MUO and MHO but no significant difference between MUO and obese subjects with MS: as consequence these parameters are equally altered as in MS as in MUO, so we can suppose that these parameters are early altered in metabolic disease of overweight and obese children but are not helpful in describing the severity of the metabolic derangement.

SBP, DBP and TG are the parameters that are statistically different in all the three groups (MS, MUO and MHO) faced each other: therefore, these parameters are able to discriminate healthy obese children from unhealthy obese and metabolically compromised obese children.

The significant difference of 2 h plasma insulin after OGTT in MS respect MUO and MHO indicate that this parameters is altered in the late stages of the disease.

Finally, other blood parameters analyzed (FPG, 2 h plasma glucose, vit. D and AST) have not statistically significant difference among the three groups studied and therefore they are not useful in the detection of potentially metabolic suffering children.

## Conclusion

Several studies hypothesize, among obese people, the existence of a favorable profile, seemingly devoid of metabolic disease. However, is not yet clear if the MHO condition is a stable condition or a state of transition to the disease. Studies in MHO children can be useful for understanding the evolution of metabolic profile in essential obesity. About that, international and Italian guidelines recommended among obese children and overweight children with family history for cardio-metabolic diseases, evaluation of blood pressure and assessment of the parameters of lipid and carbohydrate metabolism but is not known the weight that each factor has on the MS [7,24]. Peculiarity of our study is the comparison of three groups of obese children (apparently healthy, sick and in a possible state of transition): analysis of data show that a blood sample for lipid assessment and liver function together with a proper measurement and monitoring of blood pressure allows to screening overweight and obese children at early risk of metabolic disease because these parameters have a "trend in continuum" between all the three groups analyzed.

Limitation of our study is the relative smallness of the sample; besides this is an observational study: it would

be interesting to follow overtime these groups to assess modifications in metabolic profile in subsequent years with the persistence of excess body weight.

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