Is it possible a new definition of metabolic syndrome in childhood?

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Abstract. – **OBJECTIVE:** To investigate whether a group of Italian children and adolescents who were diagnosed to have metabolic syndrome (MS) according to a new ethnic age and gender specific definition had, in comparison with a control group, other signs and metabolic risk factors which are commonly associated with MS.

PATIENTS AND METHODS: The cross-sectional study population included 300 subjects (51% boys, age range 6-14 years), who were divided into 2 groups according to the presence of MS, diagnosed on the basis of 3/5 factors derived from the age and gender specific quantile distribution of MS components in a large regional Italian population survey (Calabrian Sierras Community Study, CSCS). In all subjects the following data were collected: anthropometric measures, blood pressure, liver function, C-reactive protein (hsCRP), uric acid blood levels, lipid and glucose profile. Triglycerides/HDL-cholesterol (TG/HDL-C) ratio was calculated.

RESULTS: There were 38 subjects (13%) with MS, who had higher indices of growth and fat distribution and higher blood levels of uric acid, alanine aminotransferase and gamma-glutamyl-transferase. TG/HDL ratio was higher (median 3.11 *vs.* 1.14, *p* = 0.00001) in MS subjects who had lower apolipoprotein A and higher apolipoprotein B and non-HDL-C levels. hsCRP was not different between groups.

CONCLUSIONS: Our ethnic age and gender specific definition of MS in Italian children and adolescents was able to identify in a youth group different cardiometabolic risk factors related to insulin resistance, endothelial damage and nonalcoholic fatty liver disease, which are commonly associated with MS diagnosis.

Key Words:
Metabolic syndrome, Quantile distributions, TG/HDL ratio, Risk factors, Age 6-14 years.

Abbreviations

MS = metabolic syndrome; hsCRP = high sensitivity C reactive protein; TG/HDL-C = triglycerides to HDL cholesterol ratio; CSCS = Calabrian Sierras Community Study; ROC = receiver operating characteristic.

Introduction

Childhood obesity is a worldwide epidemic. The disease is spreading from industrialized countries to the urban settings of developing countries. The global prevalence has increased markedly: more than 42 million overweight children under the age of five in 2010 (WHO website sources). Concomitantly, with the increasing prevalence of childhood obesity, the prevalence of metabolic syndrome (MS) is rising among children and adolescents[1] and reaches 50% in severely obese subjects[2]. This epidemiological scenario makes accurate diagnosis and appropriate treatment of MS in childhood an important priority for general pediatricians and specialists, although diagnostic efforts are tackled by the lack of a universally accepted definition of MS[1].

The diagnosis of MS in children depends *de facto* on the chosen definition, with higher rates of MS identification when insulin is part of the definition and child-specific cut-off points for metabolic indicators are used[3]. In this view, this definition by the International Diabetes Federation (IDF)[4] highlights the importance of waist circumference (WC) as the main component of the syndrome. In fact, WC is an independent predictor of insulin resistance, lipid levels, and blood pressure[5]. In the IDF definition[4], WC measurement is not referred to a specific cut-off point, but to values exceeding the 90th percentile of an undefined pediatric population, although "development of ethnic specific age and sex normal ranges for waist circumference" is encouraged. On the other hand, this policy is not followed in practice recommendations by IDF when defining the cut-off points of the other components of the MS: adult limits of normalcy are chosen for systolic and diastolic blood pressure (SBP, DBP), triglycerides (TG), fasting

blood glucose (FBG), HDL-cholesterol (HDL-C) of the 10-<16 years group of children and adolescents. In addition, "IDF suggests that the metabolic syndrome should not be diagnosed in children younger than 10 years, but that a strong message for weight reduction should be delivered for those with abdominal obesity."

Risk factors in growing children can be delimited only by age and gender related, percentile-based thresholds, which often do not correspond to adult thresholds, particularly in overlapping ranges of age between adolescents and adults[6]. We believe that a more sensible definition of MS in children and adolescents, including the 6-<10 year age group and inspired by IDF's own basics, should take into account the developmental challenges of all the biological variables/components of MS through adequate population surveys. Normalcy should be defined by the use of the 90th percentile as the limit of normal values for biological variables considered as cardiovascular (CV) risk factors as SBP, DBP, TG and FBG or the 10th percentile for a protective factor as HDL-C. We achieved this task publishing the Calabrian Sierras Community Study (CSCS)[7], a survey on a residential population of 1657 children and adolescents aged 6-14 years living in Calabria (Southern Italy). In that study data on anthropometric measurements, BP, FBG and lipid asset were presented. On that basis, we recently extrapolated the out-of-limit distributions of all individual components of the MS following the above mentioned use of percentiles (Table I).

We now aimed to investigate whether a group of children and adolescents attending a lipid clinic who were diagnosed to have MS, according to a new ethnic age and gender specific definition, had, in comparison with a control group, other signs and metabolic risk factors, commonly associated with MS.

Patients and Methods

The present cross-sectional study collected, between February 2009 and June 2012, data on anthropometric measures, blood pressure (BP), liver function, lipid and glucose profile of 300 consecutive children and adolescents (153 boys, 147 girls, age 9.5 ± 2.3 years, age range 6-14 years, median 10 years) who resided in the urban area of Rome, Italy. All the children underwent preliminary visits and blood tests in their own pediatrician's office and participated to a primary cardiovascular prevention screening in the Lipid Clinic of the Department of Pediatrics, Sapienza University of Rome, Italy. Parents gave their informed consent. The Local Ethical Committee approved the study protocol.

The study subjects were divided into two groups according to the presence of MS. Since that up till now there are no Italian national standards of normalcy in childhood for BP, fat distribution and lipid levels, in this study MS was diagnosed on the presence of 3 out of 5 factors defined on age and gender specific < 10% quantile distribution of HDL-C levels or > 90% quantile distributions of TG, FBG, WC and SBP or DBP in CSCS (Table I).

Anthropometric Variables

All the measurements were performed by physicians specifically trained for this project. All children enrolled in this study underwent physical examination to obtain anthropometric measures (weight, height, WC and hip circumference) according to standard guidelines[8].

Body weight was measured in light clothes and without shoes and was approximated to the nearest 0.1 kg on a mobile digital scale (Seca, Hamburg, Germany), and height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Seca, Hamburg, Germany).

WC and hip circumference were measured to the nearest 0.1 cm by a non-elastic flexible tape in the standing position. To measure the WC the tape was applied horizontally midway between the lowest rib margin and the iliac crest, while hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor. Waist/height ratio was derived.

Body mass index (BMI) was calculated in each participant as weight (kg) over squared height (m^2).

Blood Pressure Measurement

BP was measured using a mercury sphygmomanometer, with the appropriate cuff for the children's upper arm size. Three cuffs with different bladder sizes (8 × 13 cm, 9 × 23 cm and 12 × 22 cm) were used, according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents[9]. SBP was defined by the onset of the first Korotkoff sound, and DBP was indicated by the fifth Korotkoff sound (disappearance of Korotkoff sound). BP measurement was approximated to the nearest 2 mmHg. BP was

Table I. Gender and age specific distributions from the CSC Study, a Southern Italian residential cohort [7], used to define the clustered cut-off limits[8] for diagnosing metabolic syndrome in our lipid clinic attendees from a similar geographic location.

	N	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)		HDL cholesterol (mg/dl)		Triglycerides (mg/dl)		Fasting glucose (mg/dl)		Waist circumference (cm)	
		90th	95% CI	90th	95% CI	10th	95% CI	90th	95% CI	90th	95% CI	90th	95% CI
Girls (age)													
6-year old	17	104		68		76.4		86.6		82.2		73.8	
7-year old	100	109.5	100-110	70	70-75	76.9	73-80	97.6	78-115	85	83-87	74	65-79
8-year old	91	110	105-115	75	70-80	72	67-81	98.6	80-121	87.6	82-90	71.8	69-80
9-year old	89	110	105-110	70	70-80	73	69-79	103	87-121	85	82-92	78	72-81
10-year old	94	110	110-115	70	70-75	63.5	61-73	103.5	88-120	87	84-90	79	76-83
11-year old	81	110	105-115	70	70-80	68	66-74	99.8	86-109	86	84-89	75.8	71-79
12-year old	110	120	110-120	80	70-80	67.9	63-72	99.9	84-127	88.9	86-92	79.9	76-84
13-year old	114	120	120-120	80	75-80	76.5	69-81	89.5	80-111	89	87-93	83	77-87
14-year old	91	120	120-125	75	70-80	71.8	67-75	84.2	73-89	91	85-93	76	73-80
Boys (age)													
6-year old	11	116		76.4		76.4		71.6		90.2		70.6	
7-year old	90	110	105-110	77.9	72-89	77.9	72-89	102.8	84-124	89	86-94	72.9	68-85
8-year old	117	110	105-110	70	70-70	73.2	68-78	81.2	73-98	89	87-91	72.2	68-75
9-year old	122	110	110-115	70	70-80	75.8	71-82	96.2	86-116	89	87-91	74	72-80
10-year old	127	115	110-120	70	70-80	73	68-80	103.6	88-117	88	86-91	83	79-86
11-year old	81	119	110-120	70	70-75	78	71-86	108.4	95-122	90.8	89-94	79	74-83
12-year old	112	120	110-120	75	70-80	73.4	65-83	102.4	84-124	89.7	86-94	90	87-92
13-year old	121	120	120-120	75	70-80	69.8	67-77	106.8	88-139	89	87-92	84.8	82-92
14-year old	89	125	120-130	80	75-80	64	60-73	97	84-127	89	87-92	93	87-95

10th and 90th represent the percentiles in gender and age specific distributions. For diagnosing metabolic syndrome > 90th percentiles of systolic or diastolic blood pressures and triglycerides, fasting blood glucose and waist circumference were considered along with < 10th percentiles of HDL cholesterol. 3 of 5 characteristics (for blood pressure: systolic or diastolic) outside cut-off limits were needed for diagnosis. 95% CI: 95% confidence intervals of the 90th percentiles.

measured in the clinic by the same physician on the same occasion as the anthropometric measurements, while children were sitting and with the cubital fossa supported at heart level, after at least 5 min of rest. Measurements were performed in triplicate, 2 min apart, and the average value was used as the BP value for this study.

Biochemical Analyses

Blood samples were collected after an overnight fast. Blood (10 ml) was collected into a plain tube and a tube containing EDTA (1 mg/ml) to separate plasma, by centrifugation at 3,000 rpm for 15 min. FBG, plasma total cholesterol (TOT-C), TG and HDL-C were measured using standard enzymatic-colorimetric proce-

dures. LDL-C was calculated by the standard Friedewald formula. Non-HDL-C was calculated by subtracting HDL-C from TOT-C. TG/HDL-C ratio was also calculated.

Apolipoproteins A1 and B (apoA1 and apoB) were measured by nephelometry and their ratio was calculated.

Plasma levels of uric acid, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma-glutamyltransferase (GGT) and high-sensitivity C-reactive protein (hsCRP) were measured by standard methods.

Statistical Analysis

Median and 95% confidence intervals of the median were tabulated for each variable subdi-

Table II. Metabolic syndrome (MS) based on 3 of 5 components defined on age and gender specific < 10% quantile distribution of HDL-cholesterol levels or > 90% quantile distributions of triglycerides, blood glucose, waist circumference and systolic or diastolic blood pressures in CSC study [7] among 6-14 years attendees (N=300) of a pediatric lipid clinic compared to mates without MS: anthropometric and laboratory parameters.

	MS absent (n = 262; 87%)			MS present (n = 38; 13%)			Z value (Difference <>0)	p
	Count	Median	95% CI	Count	Median	95% CI		
Age (years)	262	10	10-10	38	10	9-12	0.56	0.57
Gender (girl=0; boy=1) (*)	262	1	0-1	38	1	0-1	0.56	0.57
Total cholesterol (mg/dl)	262	195	192-201	38	209	183-226	1.26	0.21
HDL cholesterol (mg/dl)	261	57	55-59	38	39	34-49	-5.35	0.00001
LDL cholesterol (mg/dl)	261	122	118-126	38	129	117-158	1.88	0.059
Non HDL cholesterol (mg/dl)	262	138	133-142	38	161	141-179	3.16	0.01
Triglycerides (mg/dl)	262	66	62-70	38	119	104-145	6.49	0.00005
Glucose (mg/dl)	247	85	83-85	38	90	86-92	4.07	0.0001
ALAT (U/l)	250	16	15-17	36	21	16-27	3.39	0.001
ASAT (U/l)	248	25	24-26	35	26	24-28	0.81	0.42
GGT (U/l)	219	11	11-12	36	14	12-16	2.64	0.01
apoA1 (g/l)	223	1.53	1.50-1.56	37	1.32	1.21-1.50	-3.67	0.001
apoB (g/l)	246	0.80	0.77-0.82	37	0.91	0.84-1.03	3.13	0.002
apoA1/apoB	223	0.51	0.49-0.54	37	0.72	0.62-0.80	5.04	0.00001
Uric Acid (mg/dl)	257	0.23	0.22-0.24	38	0.26	0.22-0.32	2.66	0.01
hs-C-reactive protein (ng/l)	219	0.80	0.68-1.12	30	0.52	0.40-1.30	-1.36	0.17
Height (cm)	252	138	134-140	38	145	143-150	2.82	0.01
Weight (kg)	251	36	34-39	38	45	37-53	2.84	0.01
Body mass index (units)	251	13	12-14	38	15	13-17	2.65	0.01
Hip circumference (cm)	244	71	69-73	37	76	68-85	2.09	0.05
Waist circumference (cm)	245	64	62-66	38	68	64-77	2.21	0.05
Waist/height (ratio)	244	0.47	0.46-0.48	38	0.48	0.43-0.52	0.27	0.78
Triglycerides/HDL (ratio)	261	1.14	1.07-1.25	38	3.11	2.44-4.61	6.53	0.00001
Systolic blood pressure (mmHg)	244	110	110-110	38	115	110-120	2.34	0.05
Diastolic blood pressure (mmHg)	244	65	60-65	38	70	65-75	2.62	0.01

(*): Boys were 51% in both MS and without MS groups. SBP = systolic blood pressure; BMI = body mass index. Disturbances of individual MS components (based on quantile distributions of CSCS) were seen for: (1) hypoHDL in 2.15% non-MS attendees versus 23.88% MS mates (*p* < 0.00001); (2) hyper Triglycerides in 16.31% non-MS attendees versus 55.22% MS mates (*p* < 0.00001); (3) hyper Blood Glucose in 25.69% non-MS attendees versus 56.72% MS mates (*p* < 0.00001); (4) hyper Waist circumference in 11.57% non-MS attendees versus 37.31% MS mates (*p* < 0.00001); (5) hyper Systolic pressure in 38.14% non-MS attendees versus 82.09% MS mates (*p* < 0.00001); (6) hyper Diastolic pressure in 22.79% non-MS attendees versus 73.13% MS mates (*p* < 0.00001).

vided according to absence or presence of MS defined following quintile distributions of its constitutive elementary characteristics described in Table I. There were indeed departures from normal distributions of the investigated variables, based on skewness, kurtosis and coefficient of variation or applying Shapiro-Wilk W test and Kolmogorov-Smirnov or D'Agostino Omnibus tests. Accordingly, Mann-Whitney U or Wilcoxon rank-sum test for difference in medians were considered with the alternative hypothesis judged based on: difference <>0. Results are shown as Z values. NCSS software version 2007 (www.ncss.com) was used. Receiver operating characteristic (ROC) curves were compared among individual components of MS and by assessing the accuracy of selected variables to index the new definition of MS adopted here, by pairwise methods using the procedures described in: www.medcalcsoftware.com. A value $p < 0.05$ was considered statistically significant.

Results

As it can be seen in Table II, there were 38 subjects (13%) with MS in our casebook, who, by definition, had significantly lower HDL-C and higher TG, FBG, WC, SBP/DBP.

The two groups had equal age and gender distribution (51% boys in both groups). All indices of growth and fat distribution were statistically higher in the MS group apart from waist/height ratio.

There were no differences between groups in TOT-C, LDL-C and hsCRP levels, whereas apoA1 and apoB were respectively significantly lower and higher in children and adolescents with MS. In the same group apoA1/apoB ratio and non-HDL-C were statistically elevated.

Uric acid, ALAT, GGT levels and TG/HDL-C ratio were statistically higher in subjects with MS.

Individual components of MS had diagnostic accuracies for MS diagnosed according to the definition adopted here, respectively providing areas under the ROC of 0.774 ± 0.0328 (95% CI 0.719 to 0.824) for DBP, 0.720 ± 0.0336 (95% CI 0.661 to 0.774) for SBP, 0.692 ± 0.0378 (95% CI 0.632 to 0.748) for WC, 0.676 ± 0.0409 (95% CI 0.615 to 0.732) for HDL-C, 0.672 ± 0.0413 (95% CI 0.611 to 0.729) for TG, 0.631 ± 0.0396 (95% CI 0.570 to 0.690) for FBG. However, significant ROC differences were seen only be-

tween DBP and FBG ($p = 0.0096$). Moreover, although TG/HDL-C ratio ROC was not significantly higher (0.688 ± 0.0404, 95% CI 0.630 to 0.732) than WC/height ratio (0.595 ± 0.0430, 95% CI 0.535 to 0.653, $p = 0.17$), using a cut-off of TG/HDL-C ratio > 1.9 enabled (Figure 1) to identify MS subjects with fairly good accuracy and 53.7% sensitivity of and 82.3% specificity.

Discussion

The ethnic age and gender specific definition of MS in Italian children and adolescents were able to identify in a youth group different pro-atherogenic risk factors extensively reported as associated with the diagnosis of MS.

The TG/HDL Ratio

TG/HDL-C ratio is a new marker of increased cardio-metabolic risk[10,11]. In adult obesity the TG/HDL-C ratio allows an early identification of subjects with insulin resistance and increased CV risk[12]. In obese children Giannini et al[11] showed a strong association between TG/HDL-C ratio and
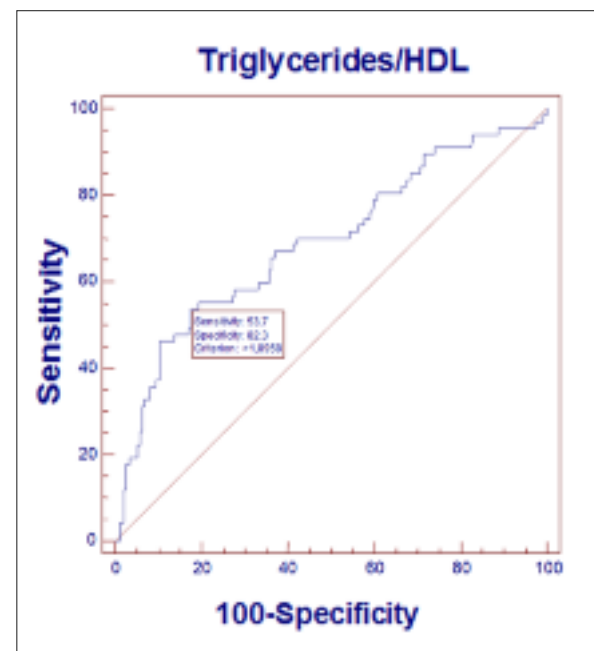

Figure 1. Receiver operatic characteristic curve of triglycerides/HDL cholesterol ratio to diagnose metabolic syndrome in our casebook of 300 children and adolescents aged 6-14 years. The criterion of > 1.9 had the highest sensitivity and the best specificity with an area under the curve equal 0.688 ± 0.0404 with 95% confidence intervals ranging from 0.630 to 0.732, representing a good accuracy.

insulin resistance, whereas Di Bonito et al[13] related TG/HDL-C ratio to concentric left ventricular hypertrophy. More recently, De Giorgis et al[14] showed a positive and strongly significant association between TG/HDL-C ratio and carotid intima-media thickness (cIMT), used as an early sign of vascular damage: a cut-off point for TG/HDL-C ratio of 1.12 had a 81% sensitivity and 49% specificity in the identification of children with values of cIMT in the upper quartile.

In our casebook the ROC curve provided good sensitivity and high specificity in identifying MS subjects for the criterion of a TG/HDL-C ratio > 1.9 and the relevance of our definition in Italian children and adolescents was testified by the highly significantly elevated ratio in the group of subjects with MS (median 3.11 vs. 1.14, *p* < 00001). Overall, diagnostic accuracy of TG/HDL-C in our casebook compares favorably with previous reports[10-13] and individually with single constituent characteristics of MS among 6-14 years children and adolescents attending our lipid clinic.

ApoA1, apoB and non-HDL-C.

The pro-atherogenic scenario was further highlighted by decreased apoA1 and increased apoB blood concentrations in this group. Whereas the reduction in apoA1, the main lipoprotein fraction associated with HDL-C, reflects a lack of anti-atherogenic protection, the increment in apoB, the main lipoprotein fraction associated with VLDL-C and LDL-C, mirrors the atherogenic lipid asset of MS, where LDL-C may not be elevated, but there is an increase in small dense LDL particles, rich in ApoB[15].

Furthermore, elevated nonHDL-C in childhood is known to be a powerful predictor of atherogenic dyslipidemia and other CV risk factors in adulthood[16].

Uric Acid

A significant elevation of acid uric levels could be considered a surrogate index of endothelial damage. In fact, blood concentrations of uric acid have a close relationship not only with other CV risk factors in obese youth[17,18], but also with cIMT itself[19]. This is not unexpected since that uric acid decreases nitric oxide production inducing endothelial dysfunction and eventually stimulating vascular smooth muscle proliferation[20].

However, we were not able to show any signs of the pro-inflammatory state associated with MS. In fact, hsCRP, which is a marker of the inflammation associated with CV events and impaired glucose tolerance or diabetes mellitus, was not significantly elevated. Nevertheless, most studies in children do not confirm the relationship between hsCRP levels and MS[21]. On the other hand, we were unable, in a previous study[22] to observe higher hsCRP in hypertensive children and adolescents attending our lipid clinic although higher but not significantly different uric acid levels were observed in comparison with normotensive mates.

BMI, hip Circumference and Waist/Height Ratio

Indices of fat distribution other than WC, that is a designated component of MS, were higher in subjects with MS, as previously reported[23]. The exception was represented by waist-height ratio that was similar between groups.

The Nonalcoholic Fatty Liver Disease (NAFLD)

Finally, children and adolescents with MS had liver function abnormalities. Even if liver structure was not investigated by ultrasound examination, the elevation of ALAT and GGT might suggest the presence of a NAFLD, which is presently considered a hepatic manifestation of MS[24].

Conclusions

A new ethnic age and gender specific definition of MS, based on quantile distributions of MS components in a large pediatric population survey[7], was able to find other signs and biomarkers of cardio-metabolic risk, commonly associated with MS, in youth group geographically related (Rome, Italy, Mediterranean area) but distinct from the original reference population (Calabrian Sierras, Italy, Mediterranean area). Therefore, our definition of MS could be employed to diagnose MS in children and adolescents from 6 to 14 years in other Mediterranean areas with similar dietary habits in the absence of local pediatric population standards. When genetic insights are accrued and the relationship between genomic mutations and MS is confirmed[25], it might become essential not only to look actively for specific gene mutations such as *DYRK1B* but also to use ethnic-based cut-off points to diagnose MS in children and adolescents. The standardized quantile approach proposed here may well be one of these methods.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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