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Estimates of insulin sensitivity and β-cell function in children and adolescents with and without components of the metabolic syndrome

Wrażliwość na insulinę i funkcja komórek β u dzieci i młodzieży z i bez cech zespołu metabolicznego

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Abstract

Introduction. The accumulation of components of the metabolic syndrome (MetS) is associated with a disturbed glucose metabolism in obese children. **Aim of study.** The aim of the present study was to evaluate the association between MetS and estimates of insulin sensitivity and β-cell function obtained from oral glucose tolerance test (OGTT)-derived indices in lean and obese children. **Material and methods.** A 2-hour OGTT was administered in 83 children aged 7-17 years. 47 children were obese and recruited from a childhood obesity clinic and 36 were lean age- and sex-matched controls. Surrogate measures of insulin sensitivity and β-cell function were assessed by the OGTT-derived indices: the Matsuda index, the insulinogenic index, and the oral disposition index. The severity of MetS was assessed by measures of waist circumference, blood pressure, and fasting levels of triglycerides, high-density lipoprotein cholesterol, and glucose. **Results.** The 83 children were allocated to one of three groups according to the number of components of MetS: the median body mass index standard deviation score was 0.2 (range -0.6-2.9) in the *low MetS risk* group (n=36), 2.8 (0.1-4.1) in the *high MetS risk* group (n=25), and 2.9 (2.1-4.4) in the *MetS* group (n=22). An increasing number of MetS components were associated with a lower insulin sensitivity and an altered β-cell function according to the Matsuda index ($p<0.0001$), the insulinogenic index ($p<0.0001$), and the oral disposition index ($p=0.005$). **Conclusions.** Children burdened by the accumulation of components of MetS exhibited a disturbed glucose metabolism as expressed by lowered peripheral insulin sensitivity and β-cell function.

Key words

Child, Glucose Tolerance Test, Insulin Resistance, Metabolic Syndrome X, Obesity

Streszczenie

Wstęp. Akumulacja komponentów zespołu metabolicznego (MetS) związana jest z zaburzeniami metabolizmu węglowodanów u otyłych dzieci. **Celem badania** była ocena związku pomiędzy MetS i wskaźnikami wrażliwości na insulinę oraz funkcją komórek β na podstawie doustnego testu obciążenia glukozą (OGTT) u dzieci szczupłych i otyłych. **Materiał i metody.** 2-godzinny test OGTT wykonano u 83 dzieci w wieku 7–17 lat. 47 dzieci było otyłych i rekrutowanych z kliniki otyłości dziecięcej, a 36 było szczupłych, dobranych wiekowo i pod względem płci. W OGTT oceniono następujące wykładniki wrażliwości na insulinę oraz funkcji komórek β: index Matsudy, index insulinogeniczny, oraz index doustnego zużycia glukozy. Ciężkość zespołu metabolicznego oceniono na podstawie pomiarów obwodu talii, ciśnienia tętniczego krwi, stężenia triglicerydów, HDL-cholesterolu oraz glukozy. **Wyniki.** 83 badanych podzielono na trzy grupy w zależności od liczby komponentów zespołu metabolicznego: w grupie niskiego ryzyka MetS mediana SDS indeksu masy ciała wynosiła 0,2 (zakres 0,6–2,9)(n=36), 2,8 (0,1–4,1) w grupie wysokiego

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ryzyka (n=25), i 2,9 (2,1–4,4) w grupie z MetS (n=22). Wzrastająca liczba komponentów zespołu metabolicznego była związana z mniejszą wrażliwością na insulinę i upośledzoną funkcją komórek β na podstawie indeksu Matsudy ($p<0,0001$), insulinogenicznego ($p<0,0001$) oraz wskaźnika doustnego zużycia glukozy ($p=0,005$). **Wnioski.** Dzieci z akumulacją komponentów MetS wykazują nieprawidłowy metabolizm glukozy, wyrażony w postaci zmniejszonej wrażliwości na insulinę i zmniejszonej funkcji komórek β.
Słowa kluczowe
dzieci, doustny test tolerancji glukozy, oporność na insulinę, zespół metaboliczny, otyłość

Introduction

Childhood obesity has reached pandemic proportions, though prevalence rates seem to have remained stable in recent years [1]. Nevertheless, due to a multitude of related co-morbidities early in life, childhood obesity comprises a major global health challenge [1,2]. Studies have shown that obesity-related type 2 diabetes (T2DM) and prediabetes are increasingly prevalent in the pediatric population [3,4], and in a recent study of 2,726 obese children and adolescents from Sweden, the prevalence of prediabetes was 17.1% [4]. In adults with prediabetes, it seems that without intervention 30–40% will progress to manifest T2DM within a period of three to four years [5]. However, several studies have demonstrated that lifestyle interventions can reduce the progression rate [6,7]. Prediabetic children and adolescents may exhibit a similar tendency and potential reversibility [8].

The metabolic syndrome (MetS) consists of a cluster of cardiovascular risk factors including an altered glucose metabolism, abdominal obesity, hypertension, and dyslipidemia [2]. The presence of MetS is known to increase the risk of cardiovascular disease and T2DM in adults [9]. Though cardiovascular disease rarely manifests in childhood, it is evident that the process of atherosclerosis starts early in life [10]. The components of MetS are also potential risk factors in the development of prediabetes [11], which underlines the importance of investigating whether metabolic derangement is associated with disturbed glucose metabolism including insulin sensitivity, and β-cell function.

In the present study, indices obtained from an oral glucose tolerance test (OGTT) were used to evaluate glucose tolerance, insulin sensitivity [12], as well as the β-cell function [13]. We hypothesized that children burdened by components of MetS may harbor some degree of impaired glucose metabolism despite not reaching the full criteria for MetS.

Aim of the study

The aim of the present study was to evaluate the association between the degree of MetS-defined metabolic derangement and estimates of insulin sensitivity and β-cell function obtained from OGTT-derived indices in obese and lean children and adolescents.

Material and methods

Subjects

This study included 83 children and adolescents aged 7 – 17 years, who were examined with a standard OGTT. The participants were included as either obese with a body mass index (BMI) standard deviation score (SDS) >2 or lean with a BMI SDS between -1 and 1. The obese children and adolescents were included from The Children's Obesity Clinic, Holbæk, Denmark [14], where they were enrolled in a multidisciplinary childhood obesity treatment program. Of 60 invited obese children and adolescents, one was excluded due to manifest diabetes measured by the fasting plasma glucose prior to the completion of the OGTT, and 12 were unable to complete the analyses, leaving 47 with completed OGTT and concomitant measures for analysis.

42 age- and sex-matched normal weight children and adolescents were included from The Danish Childhood Obesity Biobank, of whom 36 participants completed the OGTT and concomitant measures and were included in the analysis.

The study was conducted at the Children's Obesity Clinic, Department of Pediatrics, Copenhagen University Hospital Holbæk, Denmark, from June 2013 to November 2013. Informed written and oral consents were obtained from the parents prior to the study. The study was approved by the Ethics Committee of Region Zealand (protocol no. SJ-104) and the Danish Data Protection Agency.

Sampling

The children completed a standard 2-hour OGTT (1.75 g of glucose per kilogram of body weight with a maximum dose of 75 g) with measures of plasma glucose and serum insulin before and at 30, 60, and 120 minutes after oral glucose intake. The OGTT was performed after a 10-hour overnight fast and following three days of normal food intake and non-excessive exercise. Height was measured by stadiometer to the nearest 1 mm and weight wasmeasured to the nearest 0.1 kg on a Tanita medical scale, WB-110. BMI SDS was calculated by the LMS method based on a reference population of Danish children [15]. Waist circumference (WC) was measured at the umbilical level to the nearest 5 mm in a standing position and post-exhalation. Blood pressure was measured with an electronic sphygmomanometer, Omron 705IT®. After five minutes of rest in a supine position, the blood pressure was measured three times on the right upper arm and an average value was calculated from the last two measurements. Blood pressure

SDS was calculated according to an American standard population based on sex, age, and height [16].

An antecubital peripheral venous catheter was inserted, and blood samples were obtained from that.

Biochemical analyses

Plasma glucose (intra-individual coefficient of variation (CV): 2.3%), plasma triglycerides (CV: 5.2%), and plasma high-density lipoprotein (HDL) cholesterol (CV: 5.3%) were analyzed on a Siemens Dimension Vista and serum insulin (CV: 1.5%) was analyzed by enzymatic calorimetric methods on a Cobas e 601.

OGTT response

The response to the 2-hour OGTT was assessed by measuring plasma glucose and serum insulin during the OGTT, including the calculations of the following indices: The Matsuda index [17], the insulinogenic index (IGI) [18], and the oral disposition index (DI) [19]. A conversion factor of 6.00 was used between insulin in μU/L and mmol/L [20].

The Matsuda index was calculated with reduced time points: $10{,}000/\sqrt{((glucose_0(mg/dL)x\ insulin_0\ (\mu U/L))(glucose_{120}(mg/dL)x\ insulin_{120}(\mu U/L)))}$, which DeFronzo and Matsuda proposed to be in well agreement with the original calculation, and it was used as a surrogate measure of peripheral insulin sensitivity [17]. With the application of the reduced version, more children could be included since hemolysis in any of the measures of insulin or glucose would otherwise exclude the participant from having the full Matsuda index calculated. The IGI was calculated as the change in the serum insulin level (from 0 to 30 minutes) divided by the change in the plasma glucose level (from 0 to 30 minutes) [18]. The IGI is a proxy of the acute phase serum insulin response and was used for the evaluation of the β-cell function. Finally, the oral DI was calculated as the product of the IGI and the reduced Matsuda index, reflecting the relationship between the β-cell function and the peripheral insulin sensitivity [19].

The degree of metabolic derangement in the participants was assessed according to the International Diabetes Federation (IDF) definition of the metabolic syndrome in children [21], albeit with a modification in the criteria of the blood pressures and further including children below the age of ten. Children were classified as having MetS when they met the following criteria: WC $>$ 90th percentile [22,23] and two of the following criteria: fasting plasma triglycerides $\geq$ 1.7 mmol/L, fasting plasma HDL cholesterol $<$ 1.03 mmol/L, systolic or diastolic blood pressure $\geq$ 95th percentile [16] or fasting plasma glucose $\geq$ 5.6 mmol/L. In contrast to the IDF suggested adult-derived blood pressure criteria of a systolic pressure cut-off above 130 mmHg and a diastolic pressure cut-off above 80 mmHg, we suggest the 95th percentile as a more relevant criteria in a pediatric cohort due to the biological changes in blood pressure during growth and development [16].

The obese and lean children were allocated to three groups according to the degree of metabolic derangement expressed by the components of MetS. The children were categorized as *low MetS risk* if they had a WC $\leq$ the 90th percentile irrespective of prevalence of the other risk factors. Children with a WC $>$ the 90th percentile and none or one of the other risk factors were categorized as *high MetS risk*, and if the criteria for MetS were met, the children were categorized as *MetS*.

Data analysis

For the descriptive statistics, numeric non-parametric data were compared with the Kruskal-Wallis test. Variables of the OGTT-derived indices with skewed distributions (the Matsuda index, the IGI, and the oral DI) were log transformed in order to adapt to distributional assumptions for parametric analyses. The associations between OGTT-derived indices and the number of accumulated MetS risk factors were examined using one-sided ANOVA. Each component of MetS was included in a multiple regression analysis with the OGTT-derived indices as the outcome in order to identify predictors of the MetS components on the OGTT-derived indices. The multiple regression analyses were adjusted for age, sex, and BMI SDS. SAS Statistics version 9.4 was used as statistical software.

Results

The 83 (38 boys) participants had a median age of 12.0 years (range 7–17), and a median BMI SDS of 2.2 (range -0.6–4.4). 47 children were obese (21 boys) with a median BMI SDS of 2.9 (range 2.1–4.4) and a median age of 12.9 (7.2–17.9), and 36 children were normal weight (17 boys) with a median BMI SDS of 0.1 (-0.6–0.9) and a median age of 11.3 (7.3–17.8).

The 12 obese and 3 normal weight children and adolescents excluded from the study due to failure to complete the test were comparable to the included in both age, sex, and degree of obesity (data not shown).

The characteristics of the three groups *low MetS risk*, *high MetS risk*, and *MetS* are shown in table I. The three groups were significantly different in regard to age (p=0.008) and BMI SDS (p<0.0001) (table I). The distribution of boys and girls was comparable in all three groups (table I).

The evaluation of plasma glucose 120 minutes after the glucose load showed that the *MetS* group exhibited a higher post load plasma glucose compared to the group of *low MetS risk* with a mean difference of 0.96 mmol/L (95% confidence interval (CI): -1.63;-0.30, p=0.005). There were no significant differences in 120-minute glucose between the groups of *high MetS risk* and *low MetS risk* (95% CI: -0.97;0.31, p=0.3) and as well as between the groups of *high MetS risk* and *Mets* (95% CI: -1.35;0.08, p=0.08). The *MetS* group exhibited a higher mean value of fasting plasma glucose compared to the groups of *low Mets risk* (p=0.0007) and *high MetS risk* (p<0.0001) (fig. 1A).

When evaluating the OGTT-derived indices in the three groups, the *MetS* group exhibited a lower mean Matsuda index compared to the *low MetS risk* group (p<0.0001) and the *high MetS risk* group (p<0.0001) (fig. 1B). The *MetS* group and the *high MetS risk* group exhibited a higher mean IGI com-

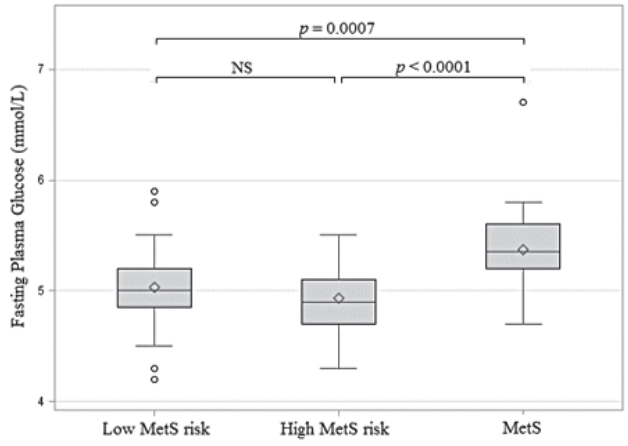

Fig. 1A. Fasting plasma glucose according to the risk level of metabolic syndrome (MetS)

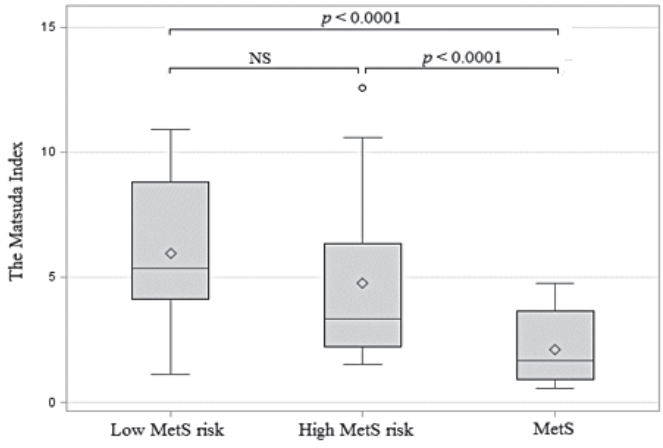

Fig. 1B. The Matsuda index according to the risk level of the metabolic syndrome (MetS)

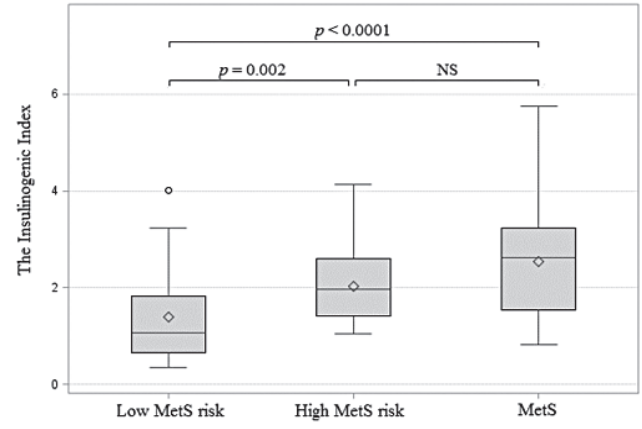

Fig. 1C. The Insulinogenic index according to the risk level of the metabolic syndrome (MetS)

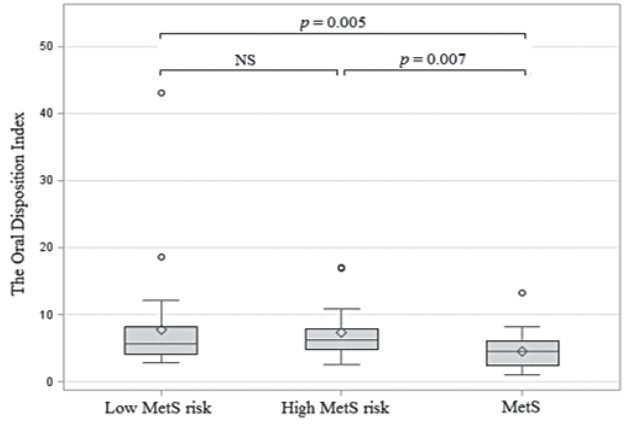

Fig. 1D. The oral disposition index according to the risk level of the metabolic syndrome (MetS)

Legends to figures

Fig. 1A. Fasting plasma glucose according to the risk level of the metabolic syndrome (MetS). ANOVA analyses of fasting glucose in the three groups ranked according to the level of metabolic derangement, n=83. Boxes represent medians and intra-quartile ranges, diamonds represent the mean values, and error bars represent ranges, though values further than 1.5 times the interquartile range are displayed as single dots. MetS, Metabolic syndrome.

Fig. 1B. The Matsuda index according to the risk level of the metabolic syndrome (MetS). ANOVA analyses of Matsuda index in the three groups ranked according to the level of metabolic derangement, n=74. Boxes represent medians and intra-quartile ranges, diamonds represent the mean values, and error bars represent ranges, though values further than 1.5 times the interquartile range are displayed as single dots. MetS, Metabolic syndrome.

Fig. 1C. The Insulinogenic index according to the risk level of the metabolic syndrome (MetS). ANOVA analyses of insulinogenic index in the three groups ranked according to the level of metabolic derangement, n=69. Boxes represent medians and intra-quartile ranges, diamonds represent the mean values, and error bars represent ranges, though values further than 1.5 times the interquartile range are displayed as single dots. MetS, Metabolic syndrome.

Fig. 1D. The oral disposition index according to the risk level of the metabolic syndrome (MetS). ANOVA analyses of oral disposition index in the three groups ranked according to level of metabolic derangement, n=66. Boxes represent medians and intra-quartile ranges, diamonds represent the mean values, and error bars represent ranges, though values further than 1.5 times the interquartile range are displayed as single dots. MetS, Metabolic syndrome.

Table I. Characteristics of 47 obese and 36 lean Danish children and adolescents grouped according to the number of MetS risk factors

	Total	Low MetS risk	High MetS risk	MetS	p
N (boys/girls)	83 (38/40)	36 (18/18)	25 (11/14)	22 (9/13)	N/A
Age (years)	12.0 (7.2-17.9)	11.3 (7.3-17.8)	12.4 (7.2-17.1)	13.6 (9.4-17.9)	0.008
BMI SDS	2.2 (-0.6-4.4)	0.2 (-0.6-2.9)	2.8 (0.1-4.1)	2.9 (2.1-4.4)	<0.0001

Data are given as frequencies or medians (range). BMI, body mass index; SDS, standard deviation score. MetS, metabolic syndrome.

pared to the *low MetS risk* group ($p<0.001$ and $p=0.0020$, respectively) (fig. 1C). Finally, the *MetS* group exhibited a lower mean oral DI compared to the *low MetS* group ($p=0.005$) and *high MetS risk* group ($p=0.007$) (fig. 1D).

Multiple regression analyses adjusted for age, sex, and BMI SDS showed that the Matsuda index was negatively associated with WC ($p=0.01$), fasting plasma triglycerides ($p<0.0001$), diastolic blood pressure ($p=0.03$), and fasting plasma glucose ($p<0.0001$), and positively associated with fasting plasma HDL cholesterol ($p=0.04$) (table II). The IGI was positively associated with fasting plasma triglycerides ($p=0.004$) and fasting plasma glucose ($p=0.009$). The oral DI was negatively associated with fasting plasma glucose ($p=0.02$) (table II).

Discussion

In this study, the children and adolescents with the most severe degree of metabolic derangement, as evaluated by the accumulation of MetS components, exhibited the lowest level of insulin sensitivity. A similar tendency for the insulin sensitivity was observed in a study of 274 obese Czech children and adolescents, where children exhibiting MetS had a lower insulin sensitivity than their peers without MetS [24]. However, in contrast to the present study, the Czech study used indices of insulin sensitivity based on fasting plasma values of insulin and glucose, which may attenuate the results and thus comparisons.

In the present study, children and adolescents who met the criteria for MetS had an augmented acute phase insulin response, as shown by a higher IGI, than the groups of *low* and *high MetS risk,* possibly related to a compensatory β-cell response due to the lower insulin sensitivity. The children with MetS in the present study exhibited a lower oral DI compared to the groups of both *low* and *high MetS risk*. This finding may be explained by an impaired capacity to compensate the lower insulin sensitivity by an increased insulin secretion from the β-cells in the group of children with MetS. This observation suggests that the children in the *MetS* group might be more prone to develop T2DM in the future than their non-MetS peers. In adults, a decreased oral DI is known to be an important predictor of progression from prediabetes to T2DM [19]. In a multiethnic cohort of 117 obese children and adolescents, Weiss *et al* found that the oral DI was a significant predictor of deterioration from prediabetes to T2DM [8], underlining the importance of applying the OGTT-derived index of the oral DI in the evaluation of insulin sensitivity in children.

In the present study, plasma glucose levels – both at fasting and after the OGTT – were not different between the groups of *low MetS risk* and *high MetS risk*. This indicates that plasma glucose alone cannot identify children in the intermediate group before the altered glucose metabolism has deteriorated further, and underlines the importance of incorporating OGTT indices in the evaluation of glucose metabolism and insulin sensitivity in daily clinical practice. This finding is in line with other studies suggesting that fasting plasma glucose may not reveal the early deterioration in glucose metabolism prior to the clinical manifestation of MetS [25,26].

The children and adolescents in the *high MetS risk* group tended to have a lower insulin sensitivity than their *low MetS risk* peers. Furthermore, in regard to the β-cell function, the *high MetS risk* group had a significantly elevated insulin response compared to the group of *low MetS risk*, possibly indicating that their β-cell function is relatively well preserved and is still able to compensate for the relative insulin resistance. Evaluating the oral DI of the *high MetS risk* group, the compensatory ability of glucose metabolism seems to be adequate still, as only the group exhibiting *MetS* could no longer compensate the decreased insulin sensitivity with an augmented insulin response.

In the present study, insulin sensitivity was negatively associated to WC, diastolic blood pressure, fasting plasma triglycerides, and fasting plasma glucose and positively associated to plasma HDL cholesterol. This correlates well with the existing literature, in which a review on metabolic risks in overweight children reported WC to be closely associated with

Table II. Relationships between OGTT-derived indices for insulin sensitivity, β-cell function, and the oral disposition index and components of the metabolic syndrome in the total group of 83 lean and obese Danish children and adolescents. Correlations were examined using multiple regression analyses adjusted for age, sex, and BMI SDS

Matsuda index				
	Estimate†	**95% CI**	**p**	**R^2**
WC	-3.1	-5.4;-0.7	**0.012**	0.40
HDL cholesterol	62.4	1.6;159.5	**0.043**	0.39
Triglycerides	-49.2	-61.1;-33.7	**<0.0001**	0.53
SBP z-score	-17.2	-31.6;0.2	0.052	0.38
DBP z-score	-24.5	-40.9;-3.6	**0.025**	0.40
FPG	-62.0	-72.4;-47.6	**<0.0001**	0.57
Insulinogenic index				
	Estimate†	**95% CI**	**p**	**R^2**
WC	1.2	-1.0;3.4	0.29	0.27
HDL	-8.3	-41.3;43.2	0.70	0.25
Triglycerides	46.8	13.6;89.8	**0.0039**	0.34
SBP z-score	15.3	-4.5;39.3	0.14	0.28
DBP z-score	21.9	-1.9;51.4	0.073	0.29
FPG	59.8	12.9;126.3	**0.0090**	0.33
Oral disposition index				
	Estimate†	**95% CI**	**p**	**R^2**
WC	-1.1	-3.5;1.2	0.34	0.25
HDL	40.5	-11.2;122.3	0.14	0.27
Triglycerides	-16.3	-37.1;11.4	0.22	0.26
SBP z-score	3.1	-15.9;26.6	0.76	0.24
DBP z-score	-7.4	-26.9;17.5	0.52	0.24
FPG	-34.8	-54.7;-6.1	**0.022**	0.30

†Reverse transformed after log transformation due to skewed distributions, thus expressing a deviation in percentage. A negative estimate indicates a negative correlation and a positive estimate indicates a positive correlation. Basic model analysis including age, sex, and BMI SDS showed R^2 =0.35 for Matsuda index, R^2=0.25 for insulinogenic index, and R^2 =0.24 for oral disposition index. BMI SDS, body mass index standard deviation score; CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; WC, waist circumference.

insulin sensitivity and where elevated fasting plasma triglycerides predicted the impairment of glucose metabolism [27]. Further, a study of 466 obese Mexican children and adolescents reported that decreased insulin sensitivity measured by the homeostatic model for insulin resistance assessment (HOMA-IR) was associated to an increased number of MetS components present [28]. In the present study, elevated β-cell function estimated by IGI was positively associated with fast-

ing plasma glucose and plasma triglycerides, and the oral DI was negatively associated with fasting plasma glucose, which indicates a reduced ability to compensate insulin resistance with an augmented insulin response.

The evaluation of glucose metabolism – and especially insulin sensitivity – is a challenge in children and adolescents as a clear consensus has not yet been defined [29]. The gold standard for determining insulin sensitivity is the hyperinsulinemic–euglycemic clamp [30], but this method is both time and resource consuming, and thus more cumbersome in clinical pediatric practice. Furthermore, another separate clamp, the hyperglycemic clamp, is needed for the evaluation of insulin secretion [30]. The OGTT is more often performed, as it is considered a clinically feasible test, even though some children may refuse to consume the oral glucose load or may experience nausea or vomiting during the test. Furthermore, OGTT-derived indices have been found suitable as surrogate measuresof insulin sensitivity [12] as well as of insulin release [13].

A limitation of the present study is the lack of pubertal staging of the participants, as the transient physiological insulin resistance during growth and development may interfere with our results.

The obese children and adolescents in this study were included from an ongoing intervention program in an obesity treatment clinic and had therefore possibly already implemented the lifestyle changes of this intervention at the time of the present examination [14]. This may have affected measures of MetS and glucose metabolism beneficially. However, this consideration does not apply to the lean participants, who were not in any sort of lifestyle intervention program.

Conclusions

In conclusion, this study of lean and obese children and adolescents observed a direct correlation between the number of components of MetS and the OGTT-derived measures of decreased insulin sensitivity and reduced β-cell function, even in study participants not reaching the criteria for MetS. We suggest that clinicians pay more attention to obese children and adolescents with metabolic derangements, even if they do not meet the criteria for MetS.

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All authors declare no conflicts of interest.

Abbreviations: BMI: Body mass index, SDS: Standard deviation score, DI: Disposition index, HDL: High-density lipoprotein, IGI: Insulinogenic index, MetS: Metabolic syndrome, OGTT: Oral glucose tolerance test, T2DM: Type 2 diabetes mellitus, WC: Waist circumference

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