

The Incidence of Metabolic Syndrome in Obese Czech Children: the Importance of Early Detection of Insulin Resistance Using Homeostatic Indexes HOMA-IR and QUICKI

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Summary

Common alimentary obesity frequently occurs on a polygenic basis as a typical lifestyle disorder in the developed countries. It is associated with characteristic complex metabolic changes, which are the cornerstones for future metabolic syndrome development. The aims of our study were 1) to determine the incidence of metabolic syndrome (based on the diagnostic criteria defined by the International Diabetes Federation for children and adolescents) in Czech obese children, 2) to evaluate the incidence of insulin resistance according to HOMA-IR and QUICKI homeostatic indexes in obese children with and without metabolic syndrome, and 3) to consider the diagnostic value of these indexes for the early detection of metabolic syndrome in obese children. We therefore performed anthropometric and laboratory examinations to determine the incidence of metabolic syndrome and insulin resistance in the group of 274 children with obesity (128 boys and 146 girls) aged 9-17 years. Metabolic syndrome was found in 102 subjects (37 %). On the other hand, the presence of insulin resistance according to QUICKI <0.357 was identified in 86 % and according to HOMA-IR >3.16 in 53 % of obese subjects. This HOMA-IR limit was exceeded by 70 % children in the MS(+) group, but only by 43 % children in the MS(-) group ($p < 0.0001$). However, a relatively high incidence of

insulin resistance in obese children without metabolic syndrome raises a question whether the existing diagnostic criteria do not falsely exclude some cases of metabolic syndrome. On the basis of our results we suggest to pay a preventive attention also to obese children with insulin resistance even if they do not fulfill the actual diagnostic criteria for metabolic syndrome.

Key words

Obesity • Metabolic syndrome • HOMA-IR • QUICKI • Children • Adolescents

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Introduction

Common alimentary obesity frequently occurs on a polygenic basis as a typical lifestyle disorder in countries of the developed world. It is characterized by the gradual onset and the development of typical complex metabolic changes. Multiple genetic polymorphisms,

which are responsible for polygenic heritability of obesity, result in the alterations of physiological regulatory mechanisms and the prevalence of accumulation mechanisms over energy expenditure. Adipose tissue is the largest endocrine organ in the human body, and when its excessive multiplication occurs, gradual but extensive metabolic changes take place (Horáková *et al.* 2010). Complex metabolic changes, acting in a mutually linked manner, are the basic cornerstones for the development of metabolic syndrome (MS) that is characterized by insulin resistance, endothelial dysfunction and dyslipidemia. However, the adult phenotypes – insulin resistance, type 2 diabetes and hypertension – could be the consequences of an insulin-resistant genotype, which manifest already *in utero* and develop in childhood (Kuneš and Zicha 2009, Kuneš *et al.* 2012). Insulin resistance development leads to the early onset of type 2 diabetes and accelerates the onset of hypertension which is later accompanied by various cardiovascular complications including the atherosclerosis (Lobstein and Jackson-Leach 2006). In recent years, obesity and metabolic syndrome have become the greatest hurdle in preventive cardiology (Ludwig 2007).

The criteria for metabolic syndrome keep developing and even the original model (Reaven 1988, 1993) is gradually being abandoned. The generally applicable definition was stipulated for the first time in 1998 by the World Health Organization (WHO 1999), and further modified in 2001 according to Adult Treatment Panel III (NCEP/ATPIII 2001). The current definition MS in adult patients was established by the International Diabetes Federation (IDF) in 2005 (Ford 2005). In 2007, the IDF criteria were modified for the pediatric population, in which MS is defined from 10 to 16 years of age in relation to the 90th BMI percentile (Zimmet *et al.* 2007). However, the MS criteria set for the adult population might be inadequate for the pediatric population (Simmons *et al.* 2010). Increased fasting glucose as a criterion of MS loses its preventive character in the pediatric population because it becomes an indicator of organ impairment. Therefore the impairment of glucose tolerance in children must be verified by means of oral glucose tolerance test.

For adult patients, the so-called euglycemic “clamp” method is considered to be the most appropriate approach, but this examination is unacceptably invasive for children, it is performed under non-physiological conditions, and this method is very demanding for both

the physicians and patients (Marinov and Pastucha 2012). The same is also true for some simplified methods that were later developed. The most frequently used is the so-called Bergman’s minimal model (Bergman 1979), which is based upon an intravenous glucose tolerance test. This technique, which evaluates the dependence between the plasma concentrations of glucose and insulin, provides the so-called insulin sensitivity index (SI). This index correlates well with the euglycemic clamp (Katz *et al.* 2000). The impairment of the homeostatic relation between plasma insulin and glucose concentrations is a symptom of insufficient insulin efficiency that can be evaluated using the so-called homeostatic model for insulin resistance assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). Both indexes are derived from fasting plasma glucose and fasting plasma insulin concentrations and they correlate reasonably with the euglycemic clamp technique (Rossner *et al.* 2010). Our pilot study (Pastucha *et al.* 2010), which evaluated the possibility of early detection of insulin resistance in obese or hypertensive children, disclosed significant differences in HOMA-IR or QUICKI indexes in these two groups as compared to healthy control population.

The aim of our study was not only to determine the incidence of metabolic syndrome in Czech obese children according the diagnostic IDF criteria, but also to consider the diagnostic value of early detection of insulin resistance (revealed by HOMA-IR and QUICKI homeostatic indexes) in obese children without metabolic syndrome.

Methods

A total of 274 children aged 9-17 years were enrolled in the study. These children are also being monitored at the Obesity Department at the Department of Exercise Medicine and Cardiovascular Rehabilitation at the University Hospital, and the Faculty of Medicine and Dentistry, Palacký University in Olomouc. There were 146 boys with a median age of 12 years, and 128 girls with the same median age. Children were referred by their pediatricians to the Obesity Department in order to reduce their abnormal body weight. Owing to the stipulated objectives of this work, only children with body mass index (BMI) over 97th percentile (Vígnerová *et al.* 2005) were monitored within the frame of this study. For each child, the following parameters were determined: blood

pressure measured by a standard mercury tonometer, using a stethoscope placed over the brachial artery for auscultation of pulse, according to the Task Force Report on High Blood Pressure in Children and Adolescents (NHBPEP 1996), waist circumferences were measured at a level midway between the lowest rib and the iliac crest and hip circumferences were measured at its widest part of the hip, BMI percentile, as well as serum concentrations of glucose, insulin, total cholesterol, triacylglycerols, high-density lipoproteins (HDL) and low-density lipoproteins (LDL) cholesterol. On the basis of fasting plasma insulin and glucose levels homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin-sensitivity check (QUICKI) indexes were calculated. HDL-cholesterol, LDL-cholesterol, blood glucose and insulin were measured on a biochemical analyzer ILAB-600 (Instrumentation Laboratory, Lexington, MA, USA), while using sets from the Bio Vendor company. These measurements were carried out at the Department of Clinical Biochemistry in University Hospital in Olomouc (according to ISO 9001: 2000).

Homeostatic indexes of insulin resistance HOMA-IR and QUICKI were calculated according to the formulae of Katz *et al.* (2000):

$$\text{HOMA-IR} = \text{fasting insulin } (\mu\text{IU/ml}) \times \text{fasting blood glucose (mmol/l)} / 22.5$$

$$\text{QUICKI} = 1 / [\log \text{fasting insulin } (\mu\text{IU/ml}) + \log \text{fasting blood glucose (mg/100 ml)}],$$

$$\text{i.e. } 1 / [\log \text{fasting insulin } (\mu\text{IU/ml}) + \log \text{fasting blood glucose (mmol/l)} \times 18.182]$$

The group of children with metabolic syndrome (MS+) included those who fulfilled the IDF criteria (Zimmet *et al.* 2007), but some criteria (BMI percentile) were used according to Weiss *et al.* (2004). First of all, there are no data for waist circumference for Czech children population so that we had to use the 97th BMI percentile (according to sex and age). Furthermore, we also used the 95th percentile as the limit for blood pressure. MS was defined as having at least three out of the five following criteria: 1) obesity, BMI above the 97th percentile for age and sex, 2) abnormal glucose homeostasis, such as fasting glucose above 5.6 mmol/l, 3) hypertension, systolic blood pressure above the 95th percentile for age and sex according to the American

Group for Children Hypertension (NHBPEP 1996), 4) dyslipidemia such as triacylglycerols above 1.2 mmol/l (in children under 10 years of age) or above 1.5 mmol/l (in children above 10 years of age), and 5) low HDL-cholesterol below 0.9 mmol/l. Children not fulfilling the MS diagnostic criteria were included to the group without metabolic syndrome (MS-).

For statistical analysis of the data, the software Statistica 8 (StatSoft, Inc.) was used. Comparative analysis between MS+ and MS- groups was carried out using the Mann-Whitney test. $P < 0.05$ level was considered to be statistically significant.

Results

The clinical characteristics of the studied population of Czech obese children are shown in Table 1. There were no major sex differences except of greater waist circumference in girls.

Symptoms of insulin resistance at QUICKI < 0.357 were identified in 86 % and at HOMA-IR > 3.16 in 53 % of the subjects. In the MS+ group, HOMA-IR limit was exceeded in 70 % children, whereas in the MS- group it was found only in 43 % children ($p < 0.0001$). Metabolic syndrome was found in 102 (37 %) of our subjects. MS occurrence was higher in boys (43 %) than in girls (31 %).

The comparison of the clinical and laboratory features between the groups with (MS+) or without metabolic syndrome (MS-) is shown in Table 2. The median BMI, waist circumference, and systolic and diastolic blood pressure were higher in the MS+ group. Serum levels of triacylglycerols were higher, and HDL-C levels were lower in the group with MS than in those without MS. Basal insulin and glucose levels as well as HOMA-IR and QUICKI were also significantly different between MS+ and MS- groups (Table 2).

Discussion

Childhood-onset obesity, left untreated, is known to significantly affect morbidity and mortality in adulthood (Daniels *et al.* 2005). In the Czech Republic, 50 % of the adult population are currently struggling with the overweight and 20 % are obese (Lajka *et al.* 2006). In the pediatric population, the incidence of common obesity is increasing steadily and currently it accounts for 95-99 % of obesity cases, while the level of pathognomonic obesity remains practically unchanged

Table 1. The clinical characteristics of the studied population of Czech obese children.

	All children (median, min/max)	Girls (median, min/max)	Boys (median, min/max)	p-value (Mann-Whitney) boys vs. girls
<i>N</i>	274	128	146	
<i>Age (years)</i>	12 (9 - 17.5)	12 (9 - 17.5)	12 (10 - 17)	n.s.
<i>SBP (mm Hg)</i>	120 (85 - 170)	120 (85 - 155)	120 (100 - 170)	<0.04
<i>DBP (mm Hg)</i>	75 (40 - 105)	72.5 (40 - 105)	75 (50 - 105)	<0.04
<i>TC (mmol/l)</i>	4.56 (2.55 - 10.15)	4.57 (3.26 - 6.78)	4.54 (2.55 - 10.15)	n.s.
<i>HDL (mmol/l)</i>	1.14 (0.5 - 2.15)	1.16 (0.5 - 1.92)	1.12 (0.57 - 2.15)	n.s.
<i>LDL (mmol/l)</i>	2.5 (0.73 - 11.44)	2.52 (0.92 - 4.9)	2.4 (0.73 - 11.44)	n.s.
<i>TG (mmol/l)</i>	1.2 (0.31 - 4.92)	1.17 (0.46 - 3.6)	1.24 (0.31 - 4.92)	n.s.
<i>Glucose (mmol/l)</i>	4.9 (2.9 - 6.5)	4.9 (3.5 - 6)	5 (2.9 - 6.5)	n.s.
<i>Insulin (μIU/ml)</i>	15.7 (2 - 54)	15.6 (2 - 54)	15.8 (2 - 52.2)	n.s.
<i>HOMA-IR</i>	3.35 (0.26 - 14.85)	3.40 (0.37 - 12.72)	3.31 (0.26 - 14.85)	n.s.
<i>QUICKI</i>	0.319 (0.264 - 0.494)	0.318 (0.269 - 0.458)	0.319 (0.264 - 0.494)	n.s.
<i>Waist (cm)</i>	84 (50 - 135)	80 (52 - 128)	87 (50 - 135)	<0.0003
<i>Hip (cm)</i>	90 (52 - 145)	88 (60 - 145)	92 (52 - 130)	n.s.

SBP – systolic blood pressure, DPB – diastolic blood pressure, TC – total cholesterol, glucose – fasting blood glucose level, insulin – fasting insulin level, HDL – high density lipoproteins, LDL – low density lipoproteins, TG – triacylglycerols, HOMA-IR – homeostasis model assessment of insulin resistance, QUICKI – quantitative insulin sensitivity check index, waist – waist circumference, hip – hip circumference.

Table 2. The incidence of metabolic syndrome in the studied population of Czech obese children and the differences in clinical characteristics between both studied subpopulations (MS+ vs. MS-).

	All children (median, min/max)	MS+ (median, min/max)	MS- (median, min/max)	p-value (MS+ vs. MS-)
<i>Gender (M/F)</i>	274 (128/146)	102 (56/46)	172 (90/82)	n.s.
<i>Age (years)</i>	12 (9 - 17.5)	13 (9.6 - 17.5)	12 (9 - 17.3)	<0.0001
<i>Body weight (kg)</i>	69.05 (32.5 - 133.8)	80.55 (33 - 133.8)	64.35 (32.5 - 127.4)	<0.000001
<i>SBP (mm Hg)</i>	120 (85 - 170)	135 (100 - 170)	120 (85 - 145)	<0.000001
<i>DBP (mm Hg)</i>	75 (40 - 105)	80 (60 - 105)	70 (40 - 100)	<0.000001
<i>TC (mmol/l)</i>	4.56 (2.55 - 10.15)	4.95 (2.98 - 10.15)	4.40 (2.55 - 6.58)	<0.00001
<i>HDL (mmol/l)</i>	1.14 (0.5 - 2.15)	0.98 (0.5 - 1.91)	1.23 (0.57 - 2.15)	<0.000001
<i>LDL (mmol/l)</i>	2.5 (0.73 - 11.44)	2.68 (1.20 - 11.44)	2.41 (0.73 - 4.90)	<0.03
<i>TG (mmol/l)</i>	1.2 (0.31 - 4.92)	1.89 (0.31 - 4.92)	1.03 (0.40 - 3.36)	<0.000001
<i>Glucose (mmol/l)</i>	4.9 (2.9 - 6.5)	5.1 (3.9 - 6.4)	4.9 (2.9 - 6.5)	<0.0002
<i>Insulin (μIU/ml)</i>	15.7 (2 - 54)	21 (2 - 52.2)	13 (2 - 54)	<0.000001
<i>HOMA-IR</i>	3.35 (0.26 - 14.85)	4.80 (0.37 - 14.85)	3.80 (0.26 - 12.72)	<0.000001
<i>QUICKI</i>	0.319 (0.264 - 0.494)	0.304 (0.264 - 0.458)	0.327 (0.269 - 0.494)	<0.000001
<i>Waist (cm)</i>	84 (50 - 135)	92 (50 - 135)	81 (52 - 134)	<0.000001
<i>Hip (cm)</i>	90 (52 - 145)	100 (52 - 145)	87 (59 - 128)	<0.000001

SBP – systolic blood pressure, DPB – diastolic blood pressure, TC – total cholesterol, glucose – fasting blood glucose level, insulin – fasting insulin level, HDL – high density lipoproteins, LDL – low density lipoproteins, TG – triacylglycerols, HOMA-IR – homeostasis model assessment of insulin resistance, QUICKI – quantitative insulin sensitivity check index, waist – waist circumference, hip – hip circumference.

(Marinov *et al.* 2012). According to the study “*Lifestyle and Obesity 2005*” (Czech Society for the Study of Obesity) (Lajka *et al.* 2006, Vignerová *et al.* 2006) about 20 % of children aged 6 to 12 years and 11 % of children aged 13 to 17 years were already overweight or obese. In the group aged 6 to 12 years, 10 % of children were overweight and 10 % were obese. The highest percentage of children with obesity (18 %) was at the age of 7 years, which can be related to the lifestyle change associated with the beginning of school. The data for the adolescent population are somewhat more favorable, because in the age group from 13 to 17 years there were only 6 % overweight children and 5 % obese children (Dagres and Anastasiou-Nana 2010, Marinov and Pastucha 2012).

Metabolic syndrome is highly prevalent within the adult population worldwide and is becoming a serious problem in the pediatric population as well (Kelishadi *et al.* 2007). Unfortunately, there is no standard definition of metabolic syndrome for the use in pediatric populations. In a recent review, Ford and Li (2008) analyzed 27 articles with 40 definitions of MS in children. The prevalence of MS among children and adolescents varies according to the definitions and the age. Some studies estimated MS prevalence as high as 30-50 % in overweight/obese children and adolescents (Cook *et al.* 2003, Weiss *et al.* 2004). The prevalence study on a cohort of U.S. overweight/obese adolescents, in which ATP III criteria were used (de Ferranti *et al.* 2004), yielded similar MS prevalence (31 %) as our study. Weiss *et al.* (2004) reported 27 % incidence of MS when a large cohort of obese children with a wide range of age was analyzed according to ATP III criteria (NCEP/ATPIII 2001). However, the subsequent analysis of this multiracial cohort according to the same criteria, that were used our study, yielded a substantially higher MS incidence, which correlated with the degree of obesity. The overall prevalence of the metabolic syndrome was 39 % in moderately obese subjects and 50 % in severely obese subjects (Weiss *et al.* 2004). These results are in agreement with the results of our work because both studies utilized identical modification of IDF criteria.

Insulin resistance is the most common metabolic alteration related to obesity and it represents an important link between obesity and other metabolic or cardiovascular complications (Sinha *et al.* 2002). Altered insulin sensitivity is thought to play a critical role in the pathogenesis of type 2 diabetes among children (Pastucha *et al.* 2010). The review by Ford and Li (2008) revealed

that 12 of 27 studies included hyperinsulinemia or increased HOMA-IR as one of the criteria for metabolic syndrome. Thus the study by da Silva *et al.* (2005) compared the MS incidence in children with normal body weight, overweight and obesity. MS incidence was 26 % in obese children in which the closest correlation with HOMA-IR values was observed. The importance of HOMA-IR index as an adequate tool for determination of insulin resistance in obese children was further supported by Makni *et al.* (2012). They reported in both sexes that HOMA-AD and HOMA-IR indexes correlated better with the majority of MS components than the adiponectin/leptin ratio. Sharma *et al.* (2011) also found that HOMA-IR is a stronger indicator of MS in children than fasting blood glucose. Thus our study further supports the validity of HOMA-IR index as an adequate tool for determining insulin resistance in obese children. Our pilot study revealed HOMA-IR value 4.58 in obese children, 2.75 in hypertensive children and 1.80 in healthy controls (Pastucha *et al.* 2010).

In conclusion, our study confirmed a high incidence of metabolic syndrome (37 %) in a group of Czech children with obesity. According to the HOMA and QUICKI indexes, insulin resistance was identified in 53 % obese children, 70 % of which were in the group of children with metabolic syndrome. However, insulin resistance was also detected among children who did not fulfill the criteria for metabolic syndrome. When we compared the groups of obese children with and without metabolic syndrome, we found a more significant difference in the value of HOMA-IR and QUICKI indexes than in the value of fasting blood glucose. We therefore believe that the insulin resistance parameters should be included among the MS diagnostic criteria for children to reduce the number of cases with falsely negative diagnosis of metabolic syndrome. We also suggest to focus the attention for children with insulin resistance even if they did not fulfill the criteria for metabolic syndrome because the early onset of preventive measures might be important for further metabolic syndrome development.

Limitations of the study

In our future research we would like to subdivide our cohort of obese children according to their age into pre- and postpubertal groups. We also intend to perform a long-term follow-up of obese MS+ and MS- children from this cohort.

Conflict of Interest

There is no conflict of interest.

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