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Metabolic syndrome in childhood: current status

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Summary

There is a significant increase in the incidence of childhood obesity all over the world which frequently leads to type 2 diabetes mellitus. Several studies have focused on the definitive criteria for diagnosis of childhood obesity and the assessment of risks for the future adverse developments. The identifying criteria for metabolic syndrome in children and adolescents have been developed. The factors most stressed in the pathogenesis of childhood metabolic syndrome are obesity and insulin resistance. The details of the metabolic processes behind this development need still to be elucidated. This paper reviews the definition, recent diagnostic criteria, incidence and pathogenesis of metabolic syndrome in children and adolescents. *(Turk Arch Ped 2011; 46: 1-5)*

Key words: Insulin resistance, metabolic syndrome, obesity

Introduction

While obesity was a rare problem in children even in USA and type 2 diabetes was observed almost never in childhood 30 years ago, currently it is being noted with amazement that 1/3 of children are obese or overweight in some cities and 1/5 of the newly diagnosed diabetes cases are type 2 diabetes in some pediatric endocrinology centers (1). However, at least 17% of adolescents are obese, but the incidence of type 2 diabetes in this age group is lower than 0.5%. Thus, the relationship between obesity and type 2 diabetes is not simple or linear. Pathogenetic relationship between obesity and type 2 diabetes has changed our viewpont of obesity: Insulin resistance is present more or less in all obese children, but obesity in a group of obese children develops as a part of the process of metabolic syndrome (MS)/prediabetes. Therefore, differentiating the obese children who have insulin resistance in the background and who carry a risk of MS/type 2 diabetes is important.

Metabolic syndrom was described as the combination of hyperglicemia, hypertension and hyperuricemia at first. Reaven (2) noted the relationship between the disorders in MS and insulin resistance using the name of Syndrome X in 1988. Definitions of WHO were made in 1998, definitions of National Cholesterol Education Program were made in 2001 and definitions of International Diabetes Federation (IDF) were made in 2005 (2-5). Studies performed in adults have shown that myocardial infarction and stoke occur in individuals with MS with a 2-3 fold higher rate compared to individuals without MS and diabetes occur with a 5 fold higher rate and it is known that MS is present in 1/4 of adult population in the world (5).

Studies performed in adults and children have suggested that marked increase in central adipose tissue accompanies the process of MS/type 2 diabetes and this tissue releases tools (including free fatty acids, TNF-alpha, IL-6, resistin) disturbing insulin signal transmission at receptor or post-receptor levels like a kind of "toxic/inflammatory area" and a vicious cycle develops between increase in the adipose tissue and insulin resistance (6,7). Although this interaction beween obesity and

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insulin resistance is known, debates continue over the issue of which one develops at first (whether insulin resistance is only a problem secondary to obesity). Information on this subject which could also be important for the process of obesity/MS/type 2 diabetes in childhood was obtained from "cell-specific insulin receptor knockout (IRKO) mouse" samples in the laboratory of Ron Kahn (6). Kahn (8) showed that adipose tissue increased only in LIRKO (liver cell specific receptor knockout) and NIRCO (neuron specific receptor knockout) mice and knockout of insulin receptors in muscle (MIRCO) and adipose tissue (FIRKO) provided protection against obesity. This model offers strong evidence that insulin resistance starts in the liver at first in obese people with metabolic risk and insulin release and consequently adipose tissue synthesis increase in response, insulin resistance starting in the central nervous system causes antagonization of leptin effect and increase in appetite, weight gain and peripheral insulin resistance and consequently firstly insulin resistance and then obesity develop in a group of obese patients and these patients are mainly candidates for MS/type 2 diabetes process (9). Based on these data, it is emphasized that pathogenesis of insulin resistance, diabetes and obesity can be viewed in the "neurocentric" sample frame, neuronal signal decrease which arises from adipose tissue and/or which is related to food may cause positive energy balance and hepatic insulin resistance, insulin resistance increases as weight gain increases and type 2 diabetes can develop at last with contribution of beta-cell failure (10).

Status in childhood

As previously mentioned investigations on MS in childhood have markedly increased in recent years. As in adults, central obesity, female gender, familial history, acanthosis nigricans, uncontrolled increase in appetite are being reported as remarkable findings. Recently, "Pediatric Metabolic Syndrome Working Group (PMSWG)" meeting was held and the results were published (11). Criteria specific for childhood and prospective risks are being discussed. If put forward in more detail, the following questions are being asked and answers are being sought: Which children with MS are candidates for type 2 diabetes? Is MS in childhood a risk for MS and type 2 diabetes in adults? What is necessary and/or important for the diagnosis of metabolic syndrome? MS criteria used in childhood: Is there a consensus? Which criterion should be used for impaired glucose metabolism?: fastin blood sugar >110 mg/dL, >100 mg/dL, 120 min>140 mg/dl in oral glucose tolerance test or hyperinsulinism? Is metabolic syndrome observed in nonobese individuals? Is screening for MS necessary in nonobese individuals? Can the transformation of the phenotype of metabolic syndrome into impaired glucose tolerance and type 2 diabetes be prevented?

Diagnosis of metabolic syndrome

In the beginning, National Cholesterol Education Program (NCEP) criteria (using childhood cut-off values) were taken as a base for the diagnosis of metabolic syndrome in childhood. Some authors used BMI Z score and consequently incidence of metabolic syndrome varied according to the criteria used (12). In analysis using American National Health Examination Survey (NHANES) 1999-2002 data, the incidence of metabolic syndrome in obese children was reported to be 44.2% according to Cook and Ford model, 12.4% according to Cruz model, 14.1% according to Caprio model and 26.2% according to NCEP criteria. Based on the same data, the incidence of obesity in individuals with a risk of obesity were found to be 7.8%, 0% and 5.8%, respectively and 1.6%, 0% and 1.1%, respectively, in normal individuals (12). In these studies, fasting blood glucose ≥100 mg/dL among NCEP criteria was used as a criterion of impaired glucose metabolism in the Cook and Ford model and fasting blood glucose ≥100 mg/dL was used in the other models. The effect of the limit of fasting blood glucose taken as ≥100 mg/dL on the difference in incidences between these models and on the finding that MS was found both in children with a risk of obesity and in normal children should be discussed (13). However, new NCEP and IDF 2005 definitions of metabolic syndrome accept the limit of impaired fasting glucose as ≥100 mg/d L and the same threshold value is used in childhood (5).

Use of impaired fasting glucose and impaired glucose tolerance individually or in combination in definition of impaired glucose metabolism and the relations of these variants with insulin resistance/insulin release is still being debated. In cases where impaired fasting glucose was defined as fasting blood glucose ≥110 mg/dl, 30% of the adult subjects with type 2 diabetes without a diagnosis had normal fasting glucose level, impaired fasting glucose (IFG) (110-125 mg/dL) was found in less than 0.08% of obese children with impaired glucose tolerance (IGT), IGT was found in 30 (4.2%) of 710 obese Italian children and IFG was found in 3 (0.4%) (two of them had also IGT), IGT and IFG were found togehter in only 27% of the sub-

jects in Pittsburgh group (14-17). Lastly, the relation of impaired fasting glucose and impaired glucose tolerance with insulin sensitivity and insulin releasing dynamics individually and in combination was investigated in obese adolescents with "hyperinsulinemic-euglycaemic and hyperglycaemic clamps" technique and peripheral insulin sensitivity was reported to be similar in normal and IFG groups, to be decreased in individuals with IGT and IGT+IFG. However, hepatic insulin resistance was reported to be increased in IFG, IGT and IFG+IFGT groups in order compared with the normal group (18). In the same study, in first-phase insulin release, glucose sensitivity was found to be decreased only in IFG, IGT and IFG+IGT groups and in the second-phase insulin release, glucose sensitivity was found only in IFG+IGT group. Thus, IFG is related to hepatic insulin resistance and glucose sensitivity in the first-phase insulin release. On the other hand, marked increase in peripheral insulin resistance and decrease in the first phase insulin release in the IGT group and decrease in insulin release in both phases together with deep insulin resistance in the IFG+IGT group are noted (18). Consequently, OGTT should be absolutely performed in children with a risk of developing type 2 diabetes without confining to fasting blood glucose (17).

Table 1. International Diabetes Federation (IDF) diagnostic criteria for metabolic syndrome

Waist circumfernece ≥94 cm, male; ≥80 cm, female	
+	
At least two out of the following:	
Triglyceride:	>150 mg/dL
HDL:	< 40 mg/dL, male
	< 50 mg/dL, female
Blood pressure:	≥130/85 mm Hg
Plasma fasting glucose:	≥100 mg/dL

Table 2. International Diabetes Federation (IDF) definitions of metabolic syndrome and risk groups in children and adolescents

6 -10 years
- Obesity: Waist circumference ≥90th percentile
- a diagnosis of MS can not be made in this age group but futher measurements should be done in children with familial type 2 diabetes, metabolic syndrome, dyslipidemia, cardio vascular disease, hypertension and obesity.

10 -16 years
- Obesity: Waist circumference ≥90th percentile (at lower values threshold value for adults)

+
- Triglyceride ≥150 mg/dL
- HDL-cholesterol <40 mg/dL
- Blood pressure ≥130 mm Hg systolic or ≥85 mm Hg diastolic
- Fasting blood glucose ≥100 mg/dL(OGTT is recommended) or known type 2 diabetes

> 16 years
- Use IDF criteria for adults.

It is known that there is a strong relationship between obesity in childhood and metabolic syndrome. According to above-mentioned four definitions, the average incidence of MS was found to be 31.3% in obese black people, 42.9% in obese white people, 0.7% in non-obese black people and 2.8% in non-obese white people (19). Although various variants are used for the definition of obesity, waist circumference reflecting visceral fat is known to be a constant determinant for insulin resistance, lipid levels and hypertension (20,21). In addition, among adolescents with the same BMI, insulin sensitivity was shown to be lower in those with more visceral adipose tissue (21). Based on this information, a waist circumference higher than the 90th percentile was used as a criterion for obestiy and recommended as a necessary criterion for the diagnosis of MS in the definition of MS in childhood developed by International Diabetes Federation (IDF) (22). The new IDF definition of MS is shown in Table 1 and 2.

Insulin resistance in children: consensus of pediatric endocrinologists

Insulin resistance is the main component of the definition of MS and plays a key role in the process between obesity and type 2 diabetes. Therefore, debates over the definition, evaluation/measurement, relation with obestiy, risk factors and treatment of insulin resistance continue. Lastly, pediatric endocrinology associations including mainly European and American Pediatric Endocrinology Associations (ESPE and LWPES) held a meeting and published a consensus text on insulin resistance (23). Main points of this consensus are summarized as follows:

1. Insulin resistance means decrease of glucose uptake in the whole body at physiologic insulin levels and this state then effects glucose and insulin metabolism. Since 75% of glucose taken is used by muscle tissue (2-3% by adipose tissue), insulin resistance is mainly determined by muscle tissue.

2. Insulin resistance is generally observed with obesity, but may also be seen in non-obese children and adults. In addition, insulin resistance may develop in physiologic conditions including pregnancy and adolescence.

3. As a response to insulin resistance chronic hyperinsulinemia develops and the negative effects of insulin resistance are related to hyperinsulinemia. However, available evidence do not support determination of insulin resistance according to fasting insulin level.

4. Standards and normal and abnormal values of insulin resistance have not been established. Some clinical properties including acanthosis nigrigans are important, tough not definitive. Fasting insulin level is not the best indicator of peripheral insulin resistance, but gives information about compensatory hyperinsulinism and hepatic insulin metabolism. Fasting insulin level is not always compatible with insulin resistance depending on the study group. In many studies, fasting insulin level is used, but these limitations should be kept in mind. Use of fasting insulin level as an index for insulin resistance can be possible following investigations in large groups and/or well defined cohorts.

5. "Euglycemic hyperinsulinemic clamp" method is the golden standard for evaluation of insulin resistance. In addition, frequently sampled intravenous glucose tolerance test (FSIVGTT) and "steady-state plasma glucose (SSPG)" tests may also be used. These tests are inconvenient. A less inconvenient method is measurement of insulin level during OGTT. Although no sufficient studies exist in children, a significant relation between OGTT and "clamp" has been reported in adults.

6. In evaluatin of insulin resistance, "Homeostasis model assessment" (HOMA)" and "Quantitative insulin-sensitivity check index (QISCI)" methods are not superior to fasting glucose in children with normal blood glucose.

7. Fasting insulin level is a weak variable for insulin sensitivity of the whole body.

8. Although the incidence of insulin resistance is not known, cardiovascular risks are known to be high in children with insulin resistance. However, screening for insulin resistance is not safe in children including obese children, since there is no easy and utilizable method for evaluation of insulin resistance and use of drugs is not needed for treatment of insulin resistance.

9. In childhood, two states are important in terms of insulin resistance: puberty and ethnicity. In puberty, insulin sensitivity is decreased by 25-50% and full recovery occurs after puberty. In black and hispanic individuals, compensatory insulin increase may occur in this period and thus risk for type 2 diabetes is increased in puberty in these ethnic groups.

10. Insulin resistance is observed in children with obesity (especially with increase in visceral/abdominal adipose tissue) and non-alcoholic fatty liver disease (NAFLD).

11. PCOS in children is manifested with insulin resistance independent of body weight.

12. Genetic and familial factors are involved in the development of insulin resistance.

13. Risk for obesity, insulin resistance and impaired glucose tolerance is increased in children exposed to poorly controlled gestational diabetes in intrauterine period.

14. In children with normal and low birth weight, increase in body weight after birth and during childhood increases the risk of insulin resistance.

15. Insulin resistance is a risk factor for prediabetes and type 2 diabetes also in children.

16. Insulin resistance increases the risk of cardiovascular disease independent of the definition of MS.

17. Diet (decreasing the amount of fat taken, eating foods of low glycemic index and eating foods containing fiber) and weight reduction improve insulin sensitivity.

18. Exercise and "fitness" improve insulin sensitivity depending on weight loss or independent of weight loss.

19. Metformine improves insulin sensitivity and is used in obese individuals with PCOS. However, it is not a recommendation for treatment of insulin resistance.

20. Correction of factors including maternal obesity, gestational diabetes, insufficient nutrition of the mother and smoking during pregnancy is important in terms of preventing obesity and insulin resistance. In addition, breastfeeding and feeding healthy solid foods after the sixth week are also important.

21. Determinig the children with a risk of obestiy in infancy and preschool childhood period and performing planned exercise programs for these children are important in terms of preventing insulin resistance.

Metabolic syndrome, Type 2 diabetes process and risk evaluation for adult life

Currently, a close relation exists between increase in type 2 diabetes in childhood and adolescence and obesity/MS process, but the process of transforming into type 2 diabetes is not sufficiently clear. On sample subjects proceeding from normal glucose tolerance to type 2 diabetes, it is emphasized that there is a strong relation between insulin resistance and "visceral obesity", hyperinsulinism developes as a response to insulin resistance in the beginning and a transformation from insulin resistance into impaired glucose tolerance and type 2 diabetes occurs when beta cell failure develops as a result of various factors (lipotoxicity, glucotoxicity…) (17,24). It was shown that insulin sensitivity decreased by 50% and first-phase insulin release decreased 75% in children with newly diagnosed type 2 diabetes and beta cell dysfunction was more severe compared to adults. Children carrying a risk for type 2 diabetes gain weight rapidly during the period of impaired glucose tolerance and this gets more severe at the time diabetes gets manifested.

Studies show that decrease in beta cell function is 2 fold faster in children during the process of development of type 2 diabetes compared to adults (17).

In a study evaluating the risks created by MS in childhood in terms of MS in adulthood and type 2 diabetes, it was shown that individuals with MS in childhood developed MS with a rate of 68.8% and developed type 2 diabetes with a rate of 15.6% in adulthood, while individuals withouth MS in childhood developed MS with a rate of 24% and developed type 2 diabetes with a rate of 5% in adulthood (25). In this study, significant indicators for MS in adults were MS in childhood, familial history of type 2 diabetes, age and increase of BMI with age; significant indicators for type 2 diabetes were MS in childhood, age, black ethnicity and familial history of type 2 diabetes (25).

Status in our country

Observations in our country show that type 2 diabetes in childhood is seen rarely yet (however, a few cases are observed in pediatric endocrinology units nowadays, while never mentioned in early years). On the other hand, the incidences of obesity and MS which are the most important risk factors for type 2 diabetes are observed to be markedly high. Recently, obesity was found with a rate of 6.8% and risk for obestiy was found with a rate of 11.5% in children of school age in Kocaeli region and MS was determined in 28.1% of obese children (26). In other studies performed in our country, MS was found with a rate of 27.2% and impaired glucose tolerance was found with a rate of 18% in obese children (27,28). In our study performed in obese children, glucose tolerance was found with a rate of 8.9%. In another study which we performed, prediabetes was found in 25.5% of children (15.2% in the whole group) with a history of type 2 diabetes in relatives (29,30).

Based on our data, it is not difficult to predict that type 2 diabetes willl be an important problem in children in the following 30 years in our country, although ethnic groups living in our country do not carry a special risk for type 2 diabetes.

Conflict of interest: None declared

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