

Metabolic syndrome in childhood

Pablo Sanjurjo Crespo*, Jose Angel Prieto Perera, Fernando Andrade Lodeiro and Luis Aldámiz-Echevarría Azuara

¹Unidad de Metabolismo, Hospital de Cruces, Plaza de Cruces s/n, Cruces-Baracaldo (Vizcaya) 48903, Spain

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Abstract

The so-called epidemic of childhood obesity has increased the interest in the metabolic syndrome (MS) due to the potential projection into adulthood. Prevalence of the MS in adolescents has been estimated to be 6.7% in young adults and 4.2% in adolescents. Figures rise up to 28.7% in overweight and obese adolescents.

The most widely accepted hypothesis links the syndrome to obesity. In the Bogalusa study, the best predictors were obesity and being in the upper quartile of basal insulin levels. Ethnic and genetic factors play a role in order to explain the syndrome in the non-obese population and the differences of interobesity.

The relationship between MS and type 2 diabetes and cardiovascular disease is well established in adults. This association can be suggested in children as well, although the syndrome in childhood urgently needs to be clearly defined. In this age group, it is also of great interest to identify diagnosis criteria of the so-called pre-MS.

Detection of the syndrome focuses mainly on obese and overweight young people. Other population groups such as newborns with low or high birth weight, infants with accelerated growth, or children of obese or with gestational diabetes mothers are at a higher risk of developing peripheral insulin resistance. The measurement of abdominal circumference can be a useful screening tool.

Physical exercise and restriction of saturated and trans fatty acids are basic for treatment. If reducing weight is necessary, a reduction of carbohydrate intake, especially for refined sugars, must be emphasised. Dietary fibre improves insulin sensitivity.

Keywords
Metabolic syndrome
Insulin resistance
Type 2 diabetes
Obesity
Children
Foetal programming

Although the metabolic syndrome (MS) was already identified 40 years ago, the agreed definition by World Health Organization (WHO) and National Cholesterol Education Program (NCEP) (Adult Treatment Panel III, ATP III) is very recent. Both definitions focus on dyslipaemia, obesity, hypertension and hyperglycaemia, but critical figures have been defined according to age, sex and sometimes the height of the individual (as described below).

The overall biochemical markers are hypertriglyceridaemia, low high-density lipoprotein-c (HDL-c), hyperglycaemia, hyperuricaemia, increased testosterone, plasminogen activator inhibitor (PAI) and fibrinogen. Associated clinical symptoms are obesity, hypertension, polycystic ovary, non-alcoholic greasy liver, acantosis nigricans, sleep apnoea and the clinical consequences are type 2 diabetes and cardiovascular disease (CVD).

Several epidemiologic studies of prevalence in adulthood have shown a physiopathologic relationship with type 2 diabetes and CVD^{1,2}. The so-called epidemic of childhood obesity has increased the interest in this syndrome due to the potential projection into adulthood.

A new concept has been defined in relation to the MS, the syndrome of insulin resistance (IR), defined as a failure of the usual levels of insulin to provide glucose to the peripheral tissues and the liver, with failure in the inhibition of very low density lipoprotein synthesis. It would be a combination of peripheral insulin resistance (PIR) and hyperinsulinaemia. Neither all obese children suffer from PIR, nor those with adequate weight are sensitive to insulin. It is likely that the so-called prudent diet, which replaces saturated fat for an excess of carbohydrates, has favourable consequences to develop this syndrome. Type 2 diabetes would start when this syndrome exhausts the possibilities of enough pancreatic insulin secretion so as to compensate for the resistance and maintain the homeostatic functions of the hormone.

Prevalence of metabolic syndrome in childhood

Diverse prevalence rates have been reported depending on the different definitions of the syndrome and analytical

*Corresponding author: Email psanjurjo@hcru.osakidetza.net

and somatometric cut-off values. Based on the definition by ATP III, prevalence has been estimated to be 6.7% in young adults and 4.2% in adolescents (males 6.1%).

Impact of obesity

Focused on the overweight and obese children and youth population, the figures rise up to 28.7% in the adolescent population (one has to bear in mind that according to NHANES III estimates, 15% of children between 6 and 19 years are overweight).

Ethnic impact

Studies carried out in the USA showed an increase of this syndrome in the Hispanic adolescent population in contrast with the Caucasian and the Afroamerican population. This increment would be associated basically to overweight, which has doubled in the last 10 years (23.4% in contrast with 12.7% in whites). Although the prevalence of obesity in Afroamerican adolescents is also high (23.6%), curiously the incidence of the MS is low. These data suggest that there is an ethnic factor independent of obesity.

Physiopathology of the metabolic syndrome

In spite of the consensus ATP III on the definition of the syndrome, its physiopathology is controversial. Generally, the most widely accepted hypothesis links the syndrome to obesity.

The Finish study about cardiovascular risk factors in childhood and youth explored predictors of the MS and established that a high basal insulin level was the best predictor. In the Bogalusa study, children between 8 and 17 years of age were followed up for a period of 11.6 years. In this study, the best predictors were obesity and also being in the upper quartile of basal insulin levels. However, the reason why some obese children develop this syndrome while others do not is still unknown. In this sense, Cruz and Goran³ have reported a study on sensitivity to insulin (measured by intravenous tolerance to glucose test) showing that after adjusting for the differences in adiposity (measured by X-ray absorptiometry), obese children with MS were 6.2% lower. It was the sensitivity to insulin and not the fat mass that correlated negatively with triglycerides and blood pressure, and positively with HDL-c. These findings suggest that it is PIR and not adiposity that is the physiopathological inductor of the syndrome. In spite of these findings, the physiopathological binomy obesity-PIR still prevails, especially when there is visceral fat accumulation.

In any case, ethnic and genetic factors play a role in order to explain the syndrome in the non-obese population and the differences of interobesity.

Genetic factors

The aetiology of PIR is multifactorial and the endocrine-metabolic factors of obtaining and expending energy are involved (energy homeostasis); hypothalamus-hypophysis factors, such as melanocortine, all hormonal factors of adipose tissue (leptin, adiponectin, resistin, TNF- α , PPAR- α , PPAR- γ) and other factors such as ghrelin, serine-protease inhibitors and, of course, insulin are involved as well.

Among the studies on the gene directly involved in PIR, it is worth mentioning: (1) genes that codify the insulin receptor itself: IRS1 and IRS2, (2) membrane genes or those that are involved in the metabolic process cascade that link the membrane receptor with the nuclear information: GLUT-4, PC-1, PI3K and (3) other genes such as PPAR- χ^2 and IGF-1R.

Factors of neonatal and infant metabolic programming

The Barker Hypothesis related epidemiologically a low gestational weight with the possibility of suffering from CVD in the future. Further investigations on this epidemiological fact showed a possible metabolic programming of intrauterine PIR (in order to send glucose from muscle to brain), thus avoiding possible cerebral damage due to the short intake (intrauterine undernourished children may have impaired glucose bioavailability).

Factors of ancestral metabolic programming

Periods of famine characteristic of our ancestors due to the glacial periods and the difficulty in collecting and hunting generated a metabolic programme with a tendency to PIR, which under those circumstances, was advantageous, but that has become a problem when faced with a combination of abundance of food and sedentarism.

A similar problem occurs with newborns with low weight for their gestational age that programme a PIR in order to palliate the deficit of glucose and drive it to the brain (favouring this path in order to avoid cerebral damage). This would make them future candidates of type 2 diabetes and CVD.

Dietary general factors

It is worth mentioning that the excessive intake of sugars, especially refined sugars of quick metabolism, and saturated and trans fatty acids as the main nutrients induces PIR.

Specific dietary factors

In 1993, Borkman *et al.*⁴ in *The New England Journal of Medicine* published a study conducted in adults. The authors showed the relationship between the fatty acid

content of long-chain polyunsaturated fatty acids (LCPs) in the muscle cell membrane and PIR: a low content generated a higher PIR. Later in 1998, Baur *et al.*⁵ (from the same Australian school) demonstrated for infants a negative correlation between the DHA content in the erythrocyte membrane and PIR.

Our research group has been mainly interested in this relationship between the polyunsaturated fatty acid content of the membranes (muscle and erythrocyte) and adipose tissue and the resistance of the peripheral receptor of insulin, and we performed a study in different paediatric ages, which awaits publication.

Relationship between metabolic syndrome, type 2 diabetes and cardiovascular disease

The relationship between MS and type 2 diabetes⁶ and CVD⁷ is well established in adults. In childhood and adolescence, this relationship could be established also by means of necropsies, in which the state of the arterial surface (measuring the affected surface in the aorta and coronary arteries) was related with atherogenic risk factors known for the population of study, which permitted the definition of the syndrome (triglycerides, blood pressure, body mass index (BMI), HDL-c)⁸.

On the other hand, high fasting glycaemia in the paediatric age is not common, even in the obese population⁹. However, there is an alteration of the latter population after intravenous loading¹⁰. It is important to point out that there is a tendency towards the projection of some constituents of the MS (obesity, triglycerides) into adulthood.

For this reason, we can say that there is a relationship between the MS and the pair type 2 diabetes/CVD in the paediatric age, which leads us to the urgent need of defining this syndrome in childhood.

Definition of metabolic syndrome in the paediatric age

There are two definitions in adults, those by NCEP ATP III, which takes into account risk factors (high blood pressure, hypertriglyceridaemia, obesity, etc.), and that by WHO, which is more conceptual, based on the simultaneous presence of other syndromes (glucose intolerance, peripheral resistance to insulin).

In the case of children, an agreement in three aspects is necessary: (1) Is the same definition valid for all paediatric ages, especially in the prepuberal and puberal children? (2) What symptoms must be included? (3) Should we use the same cut-off values as for adults?

Regarding the first question, we should remember that puberty involves a hormonal state with a tendency to PIR (anti-insulin effect of sex hormones), in a way that a definition like that of WHO should differentiate between

at least two paediatric ages (pre-puberty and puberty). Since it is simpler, if we adapt the definition to that for adults of NCEP_ATP III, we could use just one definition.

The second question finds, in some way, an answer in the first (if we use the simplification of ATP III, we should do it with the same symptoms). It is based on the fact that almost all symptoms included in the syndrome can be projected from childhood to adulthood. However, some classic symptoms in adults such as fasting hyperglycaemia are rare in childhood (it is not the same for glucose intolerance, defined as a glycaemia equal to or above 140 mg dl⁻¹, 2 hours after the loading, which is quite common in obese children). Finally, another subject for discussion is if upper percentiles of BMI or abdominal circumference must be included in the definition of the syndrome, a discussion that seems to have an affirmative answer.

The third and latter question deals with the cut-off values selected to define the syndrome in childhood. The first point is, no doubt, if the latest definition of fasting glycaemic alteration (100 mg dl⁻¹) is applicable to children. In this population, it is also necessary to define cut-off values, not only by age and sex but also by ethnic group, which would rather complicate the definition. In any case, while a definitive consensus is pending, it is possible to define some cut-off values based on those of adolescents and adults in ATP III (presence of three or more symptoms: triglycerides >109 mg dl⁻¹, HDL-c < 40 mg dl⁻¹, abdominal circumference >90th percentile (age and sex specific), fasting glycaemia >110 mg dl⁻¹ and high blood pressure >90th percentile (age, sex and height specific according to the tables of the Task Force).

The proposed criteria for adults are: WHO: diabetes/glucose intolerance/insulin resistance plus more than two of the following symptoms: dyslipaemia, hypertension, obesity and microalbuminuria.

EGIR (European Group for the study of Insulin Resistance): IR/hyperinsulinaemia plus more than two of the following symptoms: hyperglycaemia, dyslipaemia, hypertension and central obesity.

NCEP: three of the following symptoms: hyperglycaemia, hypertriglyceridaemia, low HDL-c, hypertension and central obesity.

The criteria proposed for infancy and adolescence would be:

Certainty: presence of three or more of the four classic symptoms: PIR*, obesity**, hypertension*** and hypertriglyceridaemia****

*PIR: P90 HOMA: 3.5–3.8. Euglycemic clamp, glucose loading, acute peak of insulin response.

**Not only overweight or morbid obesity

***>P90 for height (Task Force tables).

****>P90 of population values.

In paediatrics, the diagnosis criteria of the so-called pre-MS in childhood is also of great interest. The idea is making a table where biochemical, clinical and environ-

Table 1 Clinical and biochemical symptoms of the metabolic syndrome at different ages

	Clinic	Biochemistry
Neonate, sucker	AF: obesity, diabetes 2, gestational diabetes. SGA or LGA	
Pre-puberty	Acanthosis nigricans, early puberty, stretch mark in skin, elevated height	RPI&HI, IGFBP-1 (low) Cortisol, testosterone, PAI (high)
Adolescent	Pseudoacromegaly, fatty liver, amenorrhea, focal glomerulosclerosis, hirsutism	VLDL high and HDL-c low
Adult	Polycystic ovary, endothelial dysfunction, glucose intolerance, type 2 diabetes	Uric acid high, postprandial hyperglycemia Fasting hyperglycemia, glycosuria

AF – atrial fibrillation; SGA – small for gestational age; LGA – large for gestational age; RPI&HI, IGFBP-1; PAI – plasminogen activator inhibitor; VLDL – very low density lipoprotein; HDL – high-density lipoprotein.

mental would score: biochemical (high uric acid and testosterone levels in males, and high percentiles of insulin, tryglicerides or glycaemia). Clinical: polycystic ovary, acanthosis nigricans, gynecomasty, hepatic steatosis excessive weight gain, increase of the abdominal circumference. Environmental: sedentarism, excessive consumption of saccharose, trans saturated fat and sugared drinks.

Finally, there are very simplified criteria for the definition of the syndrome: Higgins *et al.*¹¹ proposed the combination of children with >33% of body fat and >71 cm of waist circumference. Moreno *et al.*¹² consider the abdominal circumference as the best predictor of the MS in childhood.

Symptomatology of the metabolic syndrome

The different biochemical and clinical symptoms that define the syndrome have been exposed in the introduction and definition sections. However, it might be useful to present the usual outbreak of the syndrome throughout the paediatric age¹³ (see Table 1).

Strategies of screening and treatment of MS in childhood

Localisation of risk population

Taking into account the parameters and cut-off values established for the definition of the syndrome in the paediatric age, it can be deduced that the detection of the syndrome focuses mainly on obese and overweight young people. However, other population groups such as newborns with low or high birth weight, infants with accelerated growth, or children of obese or with gestational diabetes mothers are at a higher risk of developing PIR¹⁴. The presence of clinical manifestations very much related with the MS, acanthosis nigricans, polycystic ovary, non-alcoholic fatty liver obliges to searching for the syndrome.

The study of a family background (type 2 diabetes, obesity, hypertension, hypertriglyceridaemia) can be an important help in the localisation of a population at

risk. The measurement of simple parameters such as abdominal circumference can be a useful tool in the population screening of these patients.

Treatment

Physical exercise is one of the pillars of treatment. It must be quotidian and intense¹⁵, and adequate to the individual possibilities. It can be adapted to a programme of exercise (for instance walk or swim for 30 min every day). Weight-bearing exercise is also helpful.

Dietetic aspects of treatment imply the restriction of saturated and trans fatty acids. If reducing weight is necessary, it must be emphasized in the reduction of carbohydrate intake, especially for refined sugars.

Dietary fibre improves insulin sensitivity by different mechanisms. It has been reported that the consumption of whole-grain cereals improves insulin sensitivity in adolescents¹⁶. Other foods such as soy protein (rich in isoflavones) and linsseed oil also improve insulin sensitivity¹⁷.

Metformin and thiazolidinediones have been used in the pharmacological treatment of the severe forms of PIR, apparently with good results^{18,19}.

For the management of dyslipaemia, fenofibrate and statines have been proposed. It is necessary to remember that the combination of both pharmaceuticals has caused occasionally serious episodes of rbdomiolisis.

Paediatric surgical treatment (intestinal bypass) is only recommended if there is risk of death due to complications of the syndrome such as sleep apnoea.

As a complementary treatment, other factors of atherogenic risk must be avoided, such as smoking or the consumption of alcohol.

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