Metabolic syndrome in the pediatric population: a short overview

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Abstract

The metabolic syndrome (MS) in adults is defined as a concurrence of obesity, disturbed glucose and insulin metabolism, hypertension and dyslipidemia, and is associated with increased morbidity and mortality from cardiovascular diseases and type 2 diabetes. Studies now indicate that many of its components are also present in children and adolescents. Moreover, the clustering of these risk factors has been documented in some children, who are at increased cardiovascular risk in adulthood. The MS is highly prevalent among overweight children and adolescents. Identifying these children is important for early prevention and treatment of different components of the syndrome. The first-line treatment comprises lifestyle modification consisting of diet and exercise. The most effective tool for prevention of the MS is to stop the development of childhood obesity. The first attempt at consensus-based pediatric diagnostic criteria was published in 2007 by the International Diabetes Federation. Nevertheless, national prevalence data, based on uniform pediatric definition, protocols for prevention, early recognition and effective treatment of pediatric MS are still needed.

The aim of this article is to provide a short overview of the diagnosis and treatment options of childhood MS, as well as to present the relationships between MS and its individual components.

Introduction

More than 20 years have passed since the first description of metabolic syndrome (MS) in adults.¹ During this time, many expert groups have proposed definitions of MS, with some common characteristics and some differences.^{2,5} The purpose of these definitions has been to determine which patients are at increased cardiovascular (CV) risk. At present the view held is that in each adult patient with a single CV risk factor, all the other known risk factors have to be looked for and individually treated.^{6,7} On the other hand, in children, till now, only one consensus-based definition of

pediatric MS has been published,⁸ although many studies have shown that MS and its components do appear in childhood.⁹ In fact, their prevalence is on the increase,^{10,11} mostly on account of obesity.^{12,13} Obesity and the closely linked insulin resistance are presumed to play a central role in the development of MS.^{14,15} Many studies have also shown that clustering of CV risk factors continues into adulthood¹⁶ and predicts the risk of future CV events and diabetes.^{17,18} In numerous epidemiological studies, the negative influence of MS on CV morbidity and mortality and on type 2 diabetes has been documented.^{19,20} On the other hand, lower CV risk and prevalence of MS have been established in children and adults with MS components in the lower normal range, independent of a positive family history of CV disease (clinical marker of genetic predisposition).^{21,22} This further indicates the important role of a healthy lifestyle in early childhood in the prevention of CV diseases.

In this review article we describe definitions of MS, discuss its pathophysiology, point out the management and treatment options, and present physiological mechanisms between MS and its constitutive elements.

Definition of metabolic syndrome

MS was first described by Reaven.¹ In subsequent years different names have been used, namely, dysmetabolic syndrome, syndrome X, cardiometabolic syndrome, deadly quartet and insulin resistance syndrome.¹⁵ Most studies performed in recent years have used definitions published by the World Health Organization (WHO)² and by the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III),³ which was later revised.⁴ A similar definition was adopted in 2005 by the International Diabetes Federation (IDF).⁵ The most often used definitions are presented in Table 1.^{2,3,5,23}

Two years later, the first consensus-based definition of MS in children was published⁸ (Table 2), whether it unifies the field remains to be seen. Namely, in pediatric studies as many as 40 different definitions of MS have been applied.²⁴ Some of them are presented in Table 3.^{11,25-27} for the whole list of studies some good reviews are available.^{24,28}

Most researchers have used adapted definitions of MS in adults, especially NCEP/ATP III³ and the World Health Organization,² with components of MS adjusted according to age and percentile values.^{25-27,29} Difficulties in defining the MS in children arise from their different growth patterns, from the influence of hormonal changes in puberty on insulin resistance and lipid profiles, and from ethnic differences.¹⁴ Additionally, there has been no universal agreement about which level of particular component to use for the criteria. Instead, values above the 85th, 90th, 95th, 97th and even 75th

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percentile for age and gender have been used (Table 3). For this reason, comparison between studies is difficult. Recently, first studies using pediatric IDF definition have been published.^{30,31}

In addition to five components of the clinical definition of MS, there are numerous associated findings, including procoagulant and proinflammatory states^{15,32} (Table 4).

Prevalence of metabolic syndrome

The prevalence of MS in adults, according to the NCEP/ATP III, was found to be around 15% in Europe³³ and 24% in the United States,³⁴ respectively, most probably due to obesity and unhealthy lifestyles in the latter. Many studies showed that MS prevalence is highly dependent on the definition used.³⁵⁻³⁷ Prevalence results of studies, comparing WHO with the NCEP/ATP III definition, were mostly similar,³⁶ whereas in most studies using the IDF definition, the prevalence was higher,³⁶ reaching even 43.4%.³⁷ The situation is similar in the pediatric population, where the increasing prevalence of obesity,¹³ as well as obesity-related diseases, such as hypertension,¹⁰ type 2 diabetes³⁸ and CV diseases,³⁹ was established. For American children, the prevalence of MS was found to be 9.2% in the period from 1988 to 1994 and 12.7% from 1999 to 2000. During this period, the percentage of children with a body mass index above the 85th percentile increased from 25.9 to 30.5%.¹¹ In most other studies, the prevalence of MS in the general pediatric population was lower for both American and other pediatric patients,^{28,40} dependent not only on definition but also on the percentile cut-offs used.⁴¹ In the study of Goodman *et al.*, prevalence, using ATP III and WHO criteria, was found to be 4.2% and 8.4%, respectively.²⁷ In studies using pediatric IDF definition, prevalence for American adolescents was found to be 4.5%³⁰ and 2.4% for Finnish adolescents.³¹ In obese children, the prevalence is 30%²⁵ and reaches 50% in extremely obese children.²⁶

Table 1. Definition of metabolic syndrome according to the World Health Organization (WHO),² the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III),³ the European Group for the study of Insulin Resistance (EGIR)²³ and the International Diabetes Federation (IDF).⁵

Component of metabolic syndrome	WHO	EGIR	NCEP/ATP III	IDF
Insulin resistance (IR)	+	+		
Fasting blood glucose (or impaired glucose tolerance) (mmol/L)	≥ 6.1 (≥7.8 or type 2 diabetes)	≥ 6.1	≥ 6.1	≥ 5.6
Waist circumference (cm) or waist / hip ratio (WHR)	Men > 0.9 Women > 0.85 (WHR)	Men ≥ 94 Women ≥ 80	Men > 102 Women > 88	Men 94 Women ≥ 80, ethnically specific values
Body mass index (kg/m ²)	> 30			
Triglycerides (mmol/L)	≥1.7	> 2.0	≥ 1.7	≥ 1.7 or specific therapy
HDL- cholesterol (mmol/L)	Men < 0.9 Women < 1.0	< 1.0	Men < 1.04 Women < 1.29	Men < 1.02 Women < 1.29 or specific therapy
Blood pressure (mmHg)	≥ 140 / 90	≥ 140 / 90	≥ 130 / 85	≥ 130 / 85 or specific therapy
Number of components	IR or impaired fasting glucose or glucose intolerance + ≥ 2 others or microalbuminuria	IR + ≥2 others	≥ 3	Central obesity + 2 others

Table 2. Definition of pediatric metabolic syndrome according to the International Diabetes Federation.

Age (Years)	Criteria for the metabolic syndrome
< 10	Obesity (waist circumference > 90 th percentile), metabolic syndrome as entity is not diagnosed
10-16	Waist circumference > 90 th percentile or adult cut-off if lower Triglycerides ≥ 1.7 mmol/L HDL-cholesterol <1.03 mmol/L Glucose ≥ 5.6 mmol/L or type 2 diabetes mellitus Systolic blood pressure ≥130 or diastolic blood pressure ≥ 85 mmHg
> 16	Adult criteria

For the diagnosis, central obesity and 2 of 4 other components must be present.

Table 3. Comparison of the metabolic syndrome criteria used in some pediatric studies.

Metabolic syndrome components	Cook <i>et al.</i> ²⁵	de Ferranti <i>et al.</i> ¹¹	Weiss <i>et al.</i> ²⁶	Goodman <i>et al.</i> ²⁷
Fasting glucose (mmol/L)	≥6.1	≥6.1	Impaired glucose tolerance	≥6.1, insulin resistance > 75 th percentile (IR)
Waist circumference or body mass index (BMI)	≥ 90 th percentile	> 75 th percentile	BMI z score > 2 for age and sex	males 102 cm females 88 cm or BMI ≥95 th percentile
Triglycerides (mmol/L or percentiles)	≥ 1.2	≥ 1.1	> 95 th percentile	≥ 1.7
HDL-cholesterol (mmol/L or percentiles)	≤ 1.04 ≤	< 1.2 (< 1.3 for boys 15-19 years)	< 5 th percentile	males ≤ 0.9 females ≤ 1.01
Blood pressure	≥ 90 th percentile	≥ 90 th percentile	≥ 95 th percentile	≥ 130/85 mm Hg
Number of components	≥ 3	≥ 3	≥ 3	IR or type 2 diabetes + 2 others

Like many other countries, we have no national prevalence data on MS in our country. This is an important task for the future. Nevertheless, we have been able to conduct a study on prevalence of MS in our children with

essential hypertension and MS was diagnosed in 19.2% (NCEP/ATPIII) and 14.4% (IDF) of hypertensives, respectively, which is comparable with other similar studies.⁴²

Pathophysiology of metabolic syndrome

In contrast to adults, pathophysiological mechanisms for MS in children have been poorly investigated. The central role of insulin resistance has been proposed, although other mechanisms are also involved.¹⁵ Resistance to the actions of insulin on carbohydrate and lipid metabolism can explain all components of MS, and in part, atherogenesis⁴³ (Table 5).

There are also an increasing number of studies investigating novel biological actions of insulin, which have shown that hyperinsulinemia itself contributes to atherogenicity.⁴³ The important role of free fatty acids in insulin resistance through specific actions that block insulin signal transduction should also be stressed. In addition, they contribute to induction of oxidative stress, inflammation and subnormal vascular reactivity.⁴⁴ According to the inflammatory hypothesis, the proinflammatory state in obesity influences insulin resistance and MS.⁴⁵ Both free fatty acids and inflammatory cytokines are involved in insulin resistance, the development of a prothrombotic and proinflammatory state, and in atherogenesis.

Obesity and metabolic syndrome

The mechanism of the influence of obesity on CV diseases and type 2 diabetes is presented in Figure 1.¹⁴ Obesity is closely related to insulin resistance, the most common abnormality seen in obesity. In obesity, enlarged adipocytes produce more proinflammatory cytokines, such as tumor necrosis factor- α and interleukin-6, and less anti-inflammatory peptides, such as adiponectin.⁴⁵ Childhood obesity which progresses into adulthood is associated with a higher morbidity and mortality than adult-onset obesity.⁴⁶ In addition to genetic factors, obesity is the most important risk factor

Table 4. Components of metabolic syndrome.

1.	Insulin resistance*
2.	Hyperinsulinemia*
3.	Obesity: visceral (central), but also generalized obesity*
4.	Dyslipidemia: high triglycerides, low HDL, small dense LDL*
5.	Adipocyte dysfunction
6.	Impaired glucose tolerance or type 2 diabetes mellitus*
7.	Fatty liver (non-alcoholic steatohepatosis, steatohepatitis)
8.	Essential hypertension: increased systolic and diastolic blood pressure*
9.	Endothelial dysfunction
10.	Renal dysfunction (micro- or macroalbuminuria)
11.	Polycystic ovary syndrome
12.	Inflammation: increased CRP and other inflammatory markers
13.	Hypercoagulability (increased fibrinogen and plasminogen activator inhibitor-1)
14.	Atherosclerosis leading to increased cardiovascular morbidity and mortality*

*Most widely incorporated into the definition of metabolic syndrome.

Figure 1. Mechanism of the influence of obesity on cardiovascular diseases and type 2 diabetes.

for MS according to all the above-mentioned mechanisms.²⁶

Abdominal obesity can be easily assessed using the simple measurement of waist cir-

cumference (WC) which is known to correlate more strongly with visceral adipose tissue than body mass index, another measure of obesity, in both adults and children, and is a strong pre-

dictor of CV risk factors.^{47,48} WC percentile nomograms in children have only recently become available for some ethnic groups,⁴⁹ but are not available for all. In addition, there is no internationally accepted classification of age specific cut-off values. To overcome these limitations, an index of the ratio between waist and height has recently been proposed for clinical use, as it does not require percentile tables. Several studies have shown that this index is a good predictor of metabolic and CV risks.^{48,50}

Dyslipidemia and metabolic syndrome

Atherogenic dyslipidemia, namely elevated triglycerides, low high-density lipoprotein (HDL)-cholesterol and small dense low-density lipoprotein (LDL), is present in MS. Atherogenic dyslipidemia is included in all published definitions of MS.^{2,3,4,5,23} Studies have shown that the risk of dyslipidemia in predicting CV risk is similar to that of high LDL-cholesterol.⁵¹ Both excessive fat deposition and genetic predisposition are involved in the development of abnormal adipose tissue. When insulin resistance blocks the inhibitory effect of insulin on adipocyte lipolysis, adipocytes increase the release of free fatty acids, which are transported to the liver. The liver incorporates free fatty acids into triglycerides, which are assembled into very low-density lipoproteins. Very low-density lipoproteins exchange triglycerides for cholesteryl esters from LDL and HDL. Most of the cholesteryl esters return to the liver in remnant particles after very low-density lipoprotein triglycerides have been hydrolyzed by lipoprotein lipase. This is regarded as a favorable effect. However, some of the cholesteryl esters may end up in the arterial wall; the proatherogenic effect. When enriched with triglycerides, both HDL and LDL are subject to lipolysis by hepatic lipase, resulting in smaller particles. Lipolyzed HDL particles, which exhibit an anti-atherogenic effect by participating in reverse cholesterol transport and by antioxidant mechanisms, are cleared more rapidly. Small dense LDL particles, formed after lipolysis of triglyceride-rich LDL, are atherogenic, probably due to increased penetration of the arterial intima and decreased antioxidant capacity.¹⁵

Hypertension and metabolic syndrome

Hypertension is one of the important components of MS. The relationship between hypertension and the MS is complex, most probably because of its multifactorial nature. An association between both hypertension and body weight and hypertension and insulin resistance has been found in children.⁵²

Angiotensin and other neurohormonal mediators of hypertension have effects on

Table 5. Metabolic effects of insulin and consequences of insulin resistance.

	Normal insulin action	Insulin-resistance state
Carbohydrates	↓ Hepatic glucose production ↑ Glucose utilization ↑ Glycogenesis	Hyperglycemia Hyperinsulinemia
Lipids	↓ Lipolysis ↓ Free fatty acids and glycerol ↑ Lipogenesis ↑ HDL ↓ Triglycerides	↑ Lipolysis ↑ Free fatty acids and glycerol ↑ Hepatic triglyceride and apoB synthesis ↓ HDL Hypertriglyceridemia ↑ Small dense LDL
Proteins	↓ Gluconeogenesis ↓ Amino acids ↑ Protein synthesis	↑ Gluconeogenesis ↑ Protein catabolism ↓ Protein synthesis
Purines	↑ Uric acid clearance ↓ Uric acid formation	Hyperuricemia

intrarenal hemodynamics and renal electrolyte handling, thus participating in blood pressure control. Increased adipocyte mass leads to increased production of angiotensinogen, providing a potential mechanism for increased blood pressure.⁵³ Adipocytes also produce angiotensin-converting enzyme and cathepsins, which effect local angiotensin conversion and catabolism, and other substances of the renin-angiotensin system.^{54,55} Angiotensin itself promotes the growth of adipocytes.⁵⁴ Free fatty acids have been shown to increase angiotensinogen production and promote oxidative stress in endothelial cells, an effect that is amplified by angiotensin.⁵³ Hyperinsulinemia may have a direct influence on elevated blood pressure by its activity on the sympathetic nervous system⁵⁶ and by sodium reabsorption in the kidney.⁵⁷ In addition, it indirectly influences mechanisms important for vasodilation through nitric oxide release and production of other vasodilators.⁵⁸ In one study of children with hypertension, MF was found in 17% of study subjects.⁴² A recent extensive assessment of various metabolic parameters in a group of children found to have primary hypertension demonstrated an association between left ventricular hypertrophy and MS in hypertensive children.⁵⁹

Proinflammatory and prothrombotic state and metabolic syndrome

Adipose tissue is not only a reservoir for energy but serves as an active secretory organ, releasing peptides and cytokines into the circulation.¹⁴ In obesity, the dysregulated production of adipocytokines has been found to participate in the development of metabolic and CV diseases.⁶⁰ Obesity is associated with subclinical chronic inflammation.⁶¹ In obese children, an elevated level of CRP has been found⁶² and its correlation with other MS components demonstrated.⁶³ Values of CRP and interleukin-6 have been found to correlate with the degree of obesity,²⁶ insulin resistance and systolic blood pres-

sure.⁶¹ Adiponectin levels, reduced in obese children, correlate negatively with body mass index, levels of triglycerides and free fatty acids and positively with insulin sensitivity.⁴⁵ The prothrombotic state in MS arises from changes in the coagulation and fibrinolytic systems, in thrombocytes and in vascular endothelial cells.³² The most extensively studied factors associated with atherogenesis are fibrinogen and plasminogen activator inhibitor-1.⁶⁴ The latter is also associated with type 2 diabetes.⁴⁵

Genetics and metabolic syndrome

Most of the components of MS, such as hypertension and hypertriglyceridemia, as well as associated abnormalities, are influenced by genetic factors. Considering only the genetics of insulin resistance, it can be said in summary, that the clustering of insulin resistance in some families has been well known for a long time.⁶⁶ Twin studies have shown that the influence of genetic factors is in the range of 47-66%.⁶⁷ Mutations in genes for insulin receptors,⁶⁸ defects in glucose transporter molecules⁶⁹ and other genetic abnormalities (e.g. generalized lipodystrophy) are associated with insulin resistance.⁷⁰ These genetic abnormalities are important for a better understanding of insulin resistance and for research into better treatment options; however, they can only explain a minor part of the genetic variability of insulin resistance. It should be stressed that several molecular pathways in energy homeostasis, lipid metabolism, the insulin receptor signaling pathway, cytokines, hormone-binding proteins and other protease regulators are responsible for the development of insulin resistance.⁷⁰

Some other important components and metabolic syndrome

In recent years, an increasing number of factors and diseases have been connected with MS and even proposed as its components. Some of them are presented in Table 4.¹⁵

Non-alcoholic fatty liver disease (NAFLD), characterized by the accumulation of large droplets of triglycerides within hepatocytes in the absence of chronic alcohol consumption, is the most common cause of pediatric liver disease.⁷¹ It has been associated with obesity and insulin resistance.⁷² In addition, studies in children have shown that it is strongly associated with multiple CV risk factors and MS, independently of body mass index, hyperinsulinemia⁷³ and the amount of visceral adipose tissue, indicating that fat accumulation in the liver may play a more important role than obesity itself in determining the metabolic risk.⁷⁴ Moreover, fatty liver may prove to be a mediator of MS.⁷⁵ It is also associated with type 2 diabetes and advanced liver disease,⁷⁵ as well as with carotid atherosclerosis.⁷⁶ The most important therapeutic measure is increasing insulin sensitivity by an attempt to lose weight. Several pharmacological agents have also been used, mostly metformin.⁷⁷

A number of studies have also reported strong association between concentrations of uric acid and the MS or its components in both adults⁷⁸ and children,⁷⁹ although uric acid is not part of any definition of the MS. Uric acid has also been associated with primary hypertension and a key role in its pathogenesis proposed.⁸⁰ Moreover, it has been shown that allopurinol lowers uric acid and blood pressure in young hypertensives.⁸⁰ In obese children, the association with carotid atherosclerosis has been demonstrated.⁸¹

Endothelial dysfunction is thought to be one of the earliest events in the development of atherosclerosis and has also been associated with MS in some studies.^{82,83} Recent insights into vascular biology have enabled us to understand the molecular mechanisms underlying endothelial dysfunction.⁸⁴ In studies, vascular endothelial function has often been evaluated using measurement of brachial artery flow-mediated dilation and detection of selected molecules, released by dysfunctional endothelium.⁸⁵ Numerous studies have been performed in obese children, and functional and structural vascular changes identified.⁸⁵⁻⁸⁷ Abdominal adipose tissue accumulation has been associated with CV risk factors and with the elastic properties of the abdominal aorta in obese children.⁸⁸

Management of children with metabolic syndrome

Follow-up of adult patients with MS has shown that, in every patient with a single CV risk factor, all the other risk factors must be sought and individually treated.⁷ At present, there are no unified consensus-based definition guidelines for the management of children with MS, an important and urgent task for the future,⁸⁹ although some preventive guidelines in cardiovascular health in childhood do

exist.⁹⁰ The American Diabetes Association has published guidelines for detection of children with type 2 diabetes. Testing is recommended for children with high-risk factors for type 2 diabetes, namely obesity, family history, high-risk ethnic groups and clinical signs associated with insulin resistance.⁹¹ We are of the opinion that the same guidelines should be applied to both adults and children. All children with essential hypertension are managed accordingly in our department.⁹² The same guidelines have been proposed by the American Heart Association.⁹³

A thorough family history and history of previous diseases and present difficulties is obtained for each child. The importance of family history, which is an independent risk factor⁹³ and which is associated with changes in risk variables from childhood to adulthood, must be stressed.^{94,95} Examination of the patient, anthropometrical measurements, blood pressure measurement and laboratory investigations are performed. Normal and cut-off values of metabolic parameters for different age groups in some populations are still problematic. For normal blood pressure values we use European measurements.^{96,97} Body mass index is used to establish obesity.⁹⁸ Normal values for waist circumference, which is a measure of abdominal obesity and directly associated with insulin resistance, have been published for some populations.^{49,99} Recently, a linear correlation between these two parameters has been found in children, so both can be used.¹⁰⁰ For dyslipidemia, most researchers and physicians use their own normal values.¹⁰¹ For glucose metabolism, in addition to fasting glucose, fasting insulin is also determined and the homeostasis model assessment of insulin resistance (HOMA-IR) calculated.¹⁰² Sometimes an oral glucose tolerance test is also performed. Measurement of fasting insulin correlates with the standard euglycemic clamp method for assessment of insulin resistance, which is expensive and time consuming.¹⁰³ The oral glucose tolerance test is a good indicator of insulin resistance.¹⁰⁴

The importance of novel CV risk factors in children has been investigated in some studies.¹⁰⁵ Although the positive predictive value of some of the parameters has already been demonstrated, their definitive place in the management of children with the MS has yet to be defined. Studies have investigated the role of CRP,^{26,61-63,105,106} interleukin-6,^{26,61} adiponectin,^{45,105,107,108} plasminogen activator inhibitor-1,⁶⁵ leptin,^{105,109} homocysteine¹¹⁰ and others factors.

Treatment of children with metabolic syndrome

MS and related diseases are an important public health problem. Therefore, for optimal detection and management of patients, a glob-

al program is needed.¹¹¹ Preventive measures must be instigated in childhood, that is, healthy lifestyle education, with emphasis on healthy nutrition and physical activity. The best prevention is prevention of the development of obesity. Measurements of body weight, body height and blood pressure are recommended from the age of three years.¹¹¹ With such management for each individual, CV risk factors will be ascertained at an early stage, the total CV risk determined and treatment started when necessary. When one or more CV risk factors are demonstrated in a child, treatment and follow-up are started. The basic treatment always consists of non-pharmacological measures, namely, lifestyle modification with regular physical activity, healthy nutrition, and maintenance of the recommended body weight. This is a healthy lifestyle, applicable to everybody. For healthy nutrition, the daily energy intake has to be reduced and adjusted to body weight. The daily diet must contain all essential components of the important foodstuff groups in five daily portions. The main aims of proper nutrition are appropriate calorie intake, optimal nutrition for health maintenance and normal growth, and maintenance of healthy nutrition habits throughout life. Fat and protein intake must be adapted to the age of the child (fat: for children from 1-3 years old 30-40% of daily calories, for older children 25-30%; protein: from 1-3 years old 5-20%, for older children 10-30%). Carbohydrates should be included in the range of 45-65%. Saturated fat must be restricted (<10%), as well as cholesterol (<300 mg /day), salt (<6 g/day) and simple sugars. Food must contain enough fiber (age of the child + 5 g/day).⁹⁰

Lack of physical activity is one of the important causes of the MS. Therefore, regular exercise is vital. For improvement in insulin sensitivity, at least 30-60 minutes of aerobic exercise daily is recommended.^{90,112} In addition, exercises for strength, which diminish insulin resistance, enlarge muscle mass and reduce visceral adipose tissue, are advised.¹¹³ Regular physical activity can improve insulin sensitivity by 40%.¹¹⁴ It has been demonstrated that eight weeks of aerobic exercises improve strength, values of HDL cholesterol and endothelial function.¹¹⁵ Additionally, sedentary activities must be reduced to less than two hours per day.¹¹⁶ Physical activity and diet undoubtedly play important roles in MS. However, research with precise measurements of exercise, diet and metabolic outcomes is needed.

It has been shown that tobacco exposure independently influences the development of MS. Therefore, prohibition of smoking is essential.¹¹⁷

Both parents and children must be counseled and educated. The whole family must

change their lifestyle habits, because CV risk factors cluster in families as a result of unhealthy lifestyle and genetic factors. Regular follow-up, education, support and stimulation are necessary.

Management and treatment of children with MS and its components also include various intervention programs. School-based programs are a notable example, highlighting the importance of developing a favorable environment that promotes balanced eating behaviors and extra-curricular physical activity.¹¹⁸ Studies also support family-based programs.¹¹⁹

We should also stress the importance of psychological aspects of MS in children. It seems that MS and depressive symptoms are linked in both directions. Namely, findings suggest that psychological characteristics, especially depression, hostility and anger, may increase the risk for the MS.¹²⁰ On the other hand, it has been shown that MS in childhood predicts depressive syndromes in adulthood.¹²¹ Therefore, psychosocial prevention and treatment interventions have to be included in the management of these patients.

If non-pharmacological measures are unsuccessful, drug treatment should be considered.

Pharmacological treatment of obesity is limited. Sibutramin is effective, but its usage is associated with side effects.¹²² Orlistat treatment is approved for treatment of obese adolescents.¹²³ In several studies, the efficacy of metformin was demonstrated in children with MS, but its definitive role must be evaluated in further studies, in particular its long-term efficacy and safety.^{124,125} Surgical treatment is limited to patients with a body mass index above 40 kg/m² and with associated diseases such as obstructive apnea, type 2 diabetes and pseudotumor cerebri.¹²⁶

Treatment of type 2 diabetes in adolescents is the same as in adults.^{127,128} In one study, 90% of patients with the MS and type 2 diabetes were treated with medications for blood sugar control, 40% with antihypertensive medications, and 10% with medication for fat reduction.¹²⁸

Guidelines for pharmacological treatment of hypertension include symptomatic hypertension, hypertensive target organ damage, stage 2 hypertension, stage 1 hypertension not improving after non-pharmacological measures, and hypertension with associated type 2 diabetes.^{129,130} As first-line treatment, inhibitors of the renin-angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) or calcium channel blockers are recommended. The former are the first-line treatment in patients with associated type 2 diabetes or renal disease, especially if proteinuria is present.^{131,132}

Treatment of dyslipidemia is started with a low fat diet, especially with low saturated fat

and cholesterol, a high fiber intake, addition of phytosterols, body weight control and regular physical activity. If these measures are unsuccessful, treatment with medications, e.g. statins is indicated, if there are no contraindications.¹³³ Well controlled studies of the efficacy, short-term safety and benefit of the statins have been conducted in children¹³⁴ and recently guidelines for treatment have been proposed.^{135,136} However, for optimal treatment of children with the MS, future studies, especially prospective studies, are needed.¹³⁷

Conclusion

CV risk factors, comprising the MS, do appear in childhood, eventually progress in adulthood, and are associated with higher CV morbidity in adults. In all children with a single CV risk factor, all other known risk factors should be determined. Each child with a single detected CV risk factor must be treated individually, initially with non-pharmacological treatment interventions. Children with several CV risk factors are at higher risk, necessitating meticulous follow-up and treatment. Children with MS components in the lower normal range are at a lower CV risk, indicating the need for healthy lifestyle promotion in early childhood. It should be stressed that primary care doctors and nurses play an important role in CV prevention and detection of individuals with a higher CV risk. The MS must not be just a new pediatric syndrome, but it should represent a challenge for better prevention strategies.

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