Chapter

Cardiovascular Risk Factors in Children

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Abstract

Cardiovascular morbidity and mortality are still increasing in developed countries with emphasis on the obesity epidemic. Children and young adults are no exception. With modern lifestyle, traditional cardiovascular risk factors, such as hypertension, obesity, dyslipidemia, insulin resistance, kidney damage, are increasingly present in children leading to premature cardiovascular events in adult life. Cardiovascular risk factor can accelerate naturally progressing atherosclerosis, which should be prevented to facilitate quality and longevity of life. Primary and primordial prevention in the pediatric population are of utmost importance. However, if a cardiovascular risk factor is already present, frequent monitoring of possible development of other cardiovascular risk factors and evaluation of end organ damage should be implemented to intervene in time.

Keywords: atherosclerosis, obesity, hypertension, dyslipidemia, insulin resistance, kidney damage, prevention

1. Introduction

Atherosclerosis, a common denominator for all cardiovascular diseases (CVD), is a complex process that starts in fetal life, and its natural course is a result of interplay between genetic and environmental factors [1]. Clinical manifestations of atherosclerosis, including coronary artery disease, cerebrovascular disease and peripheral arterial disease, will occur in two thirds of men and half of women after age 40 [2]. However, a positive association of coronary atherosclerosis and atherosclerosis in abdominal aorta with classic cardiovascular risk factors, such as hypertension, obesity, dyslipidemia and impaired glucose tolerance, has been shown already in adolescents and young adults [3]. Earlier incidence of CVD in at-risk groups of children has been suggested [4].

In recent decades, the cardiovascular risk burden has increased largely due to the obesity epidemic, contributing to the fact that now CVD are globally the leading cause of death. Since 1975, prevalence of obesity more than quadrupled among children and adolescents with an increased likelihood of becoming an adult with obesity [5, 6].

In this chapter, traditional cardiovascular risk factors in children are reviewed with proposed comprehensive management.

2. Obesity

The obesity epidemic in children is a well-known fact in recent decades and still a growing issue in some countries that needs to be tackled accordingly. Adipose tissue, an active endocrine organ, is closely involved in production of atherogenic adipokines, oxidative stress and chronic inflammation, that altogether promote atherosclerosis. Therefore, the presence of obesity alone is a risk factor for CVD [7]. Mostly, it is due to sedentary lifestyle, inappropriate food habits and genetic susceptibility, and rarely a consequence of endocrine (e.g. hypothyroidism, Cushing syndrome, hypothalamic obesity, persistent hyperinsulinism, etc), syndromic (Alström, Bardet-Biedl, Prader Willi, Beckwith-Wiedemann, Carpenter, Cohen, Albright hereditary osteodystrophy, etc.) or monogenic causes (defects in genes encoding melanocortin 4 receptor (MC4R), leptin (LEP), leptin receptor (LEPR), pro-opiomelanocortin (POMC), etc.) [8].

Obesity and overweight diagnosis are based on anthropometric measurements and body mass index (BMI) calculation. Due to the growth and development there is no single cut-off point to define obesity in children, but is dependent on age and sex. Several curves that give BMI distribution as a function of age and sex have been established [8]. Body fat can also be estimated with dual energy X-ray absorptiometry, bioelectrical impedance, computed tomography and magnetic resonance imaging of abdomen, measurement of skinfold thickness at multiple sites, air displacement plethysmography and stable isotope dilution techniques, which apply to newer methods and future perspectives in obesity assessment [9]. Waist circumference is another anthropometric measurement that correlates well with obesity and is useful in determination of central obesity, correlating even more strongly with several obesity complications, such as insulin resistance, dyslipidemia and non-alcoholic fatty liver disease [10].

Complications of obesity in children and adolescents are numerous and are in part responsible for further cardiovascular damage. They can be categorized by organ systems: cardiovascular (hypertension, left ventricular hypertrophy, atherosclerosis), metabolic (insulin resistance, dyslipidemia, metabolic syndrome, type 2 diabetes), pulmonary (asthma, obstructive sleep apnea), gastrointestinal (non-alcoholic fatty liver disease, gastroesophageal reflux), skeletal (tibia vara, slipped capital-femoral epiphysis), psychological, other (polycystic ovary syndrome, pseudotumor cerebri) [11].

Lifestyle changes are the cornerstone of obesity management and are partly age dependent. Young infants up to two years of age with high body weight should have age appropriate amounts of formula, preferably should be breastfed, and should not be given sweetened beverages, fast food and desserts, should not have any screen of any kind, should have at least 12 hours of sleep a day, and should be allowed to be as active as possible. A toddler, aged from two to four, should have a balanced diet, should not be offered sugar sweetened beverages and fast food, size of the portion should be age appropriate and they should have a routine sleep pattern. Screen time should be kept to a minimum. It is important to stress that parents are role models for children and should model the eating behavior they want their child to have. A good meal hygiene with family based meals is recommended. Children, aged 5–9, should have a balanced diet with the exclusion of sweetened beverages and fast food, they should start to be involved in organized sports along with active play. At least sixty minutes of moderate physical activity is recommended. Screen time should be limited to academic requirements. With further growth and puberty, management evolves. Mostly, recommendations are similar, however, in adolescents skipping meals with overindulgence at the

next meal or eating mostly in afternoon or evening can become an inappropriate habit leading to excess calories intake. Regular exercise routine of sixty to ninety minutes per day is recommended. With modern technologies, which in this age group are unavoidable, progress can be tracked and comparison can sometimes be encouraged between peers [12].

As parents are strong role models for children, especially younger, a family oriented approach with lifestyle changes for the whole family is recommended [12].

Pharmacological treatment of obesity in children is discouraged, however, a few studies with metformin and orlistat showed some success with weight loss, but small or none for cardio-metabolic complications [13].

3. Hypertension

Historically, hypertension was believed to be a rare disease in children, mostly due to secondary causes, however, in the past two decades, its prevalence increased significantly, mostly due to obesity, and was estimated from 4.3% among children aged 6 years to 3.3% among those aged 19 years and peaked at 7.9% among those aged 14 years [14].

In children, physiologically, blood pressure increases with age and body size, making it impossible to define a single blood pressure level to establish hypertension, as in adults. Therefore, the definition is based on the normal distribution of blood pressure in healthy children. Hypertension is defined as systolic or diastolic blood pressure above 95th percentile for sex, age and height measured on at least three separate occasions. High-normal blood pressure is defined as above 90th, but less than 95th percentile. For boys and girls, aged 16 or above, the definition is as in adults. In addition, reference values for sex, age and height of ambulatory blood pressure measurement have been obtained from different European populations and provide useful information for diagnosis and management of hypertension. The blood pressure cuff must be appropriate to the size of the child [15, 16].

Secondary hypertension is more frequent in the pediatric population, however, the prevalence varies between studies and has yet to be confirmed. The causes of secondary hypertension are numerous and should be sought for systematically depending on history, examination and clinical results. In brief, they are presented in **Table 1** [16]. Some syndromes, such as Williams's, Turner's and Leigh's, have also been associated with hypertension [16].

After a thorough diagnostic work-up, secondary causes need to be treated appropriately. If none can be established, the diagnosis of essential hypertension is confirmed. Usually, essential hypertension is present among older children with a strong family history of hypertension [16].

First-line treatment, especially in obese, is lifestyle intervention with salt restriction and weight loss. Pharmacological treatment is indicated in hypertensive children unresponsive to lifestyle modifications, as well as in children with symptomatic hypertension, secondary hypertension, target organ damage, diabetes mellitus or chronic kidney disease [17, 18]. Antihypertensive treatment is started with the lowest dose of a single drug and titrated if needed until maximum recommended dose is reached. If blood pressure is still elevated, the second drug can be added and up-titrated. The choice of particular antihypertensive drug is partly dependent on underlying etiology, partly on other relevant factors, such as end organ damage, concurrent disorders, side effects and clinician's preference [17, 18].

Etiology subgroup	Possible underlying etiology
Immunological	Systemic lupus erythematosus Juvenile ankylosing spondylitis Antineutrophil cytoplasmic antibodies-associated vasculitis
Cardiovascular	Coarctation of aorta Atrioventricular malformation Renal artery stenosis
Endocrine	Hypo- and hyperthyroidism Adrenal neuroblastoma
Gastrointestinal	Gastroschisis
Hematological	Sickle cell disease
Medications related	Steroids Central stimulants Adrenocorticotropic hormone
Neurological	Severe intraventricular hemorrhage Hydrocephalus Brain tumor Neural tube defect Arnold Chiari malformation
Renal	Hydronephrosis Nephrotic syndrome Glomerulonephritis Renal dysplasia Cystic renal disease
Respiratory	Bronchopulmonary dysplasia Chronic lung disease Sleep disordered breathing related (e.g. obstructive sleep apnea)

Table 1.
Causes of secondary hypertension in children.

4. Dyslipidemia

Dyslipidemia is a known risk factor for atherosclerosis and should be identified in youth to intervene in time and to reduce not only future CVD disease [19], but also arterial ischemic stroke in children, where dyslipidemia and hypertriglyceridemia were found to be more prevalent [20].

Commonly, lipid screening includes measurement of total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides. Additionally, several other lipoproteins, such as apolipoprotein A1 and B can be evaluated and provide further information on cardiovascular risk.

The prevalence of dyslipidemia is increasing due to increasing obesity, where almost in a half of children with obesity, a type of dyslipidemia (hypertriglyceridemia, lowered HDL, elevated LDL) is present [21]. School children, who are overweight, are 2.4 to 7.1 more likely to have elevated total cholesterol, LDL and triglycerides in comparison to lean peers [22].

Dyslipidemia in children can be a consequence of inherited dyslipidemia syndrome. Familial hypercholesterolemia, a monogenic, autosomal dominant disorder, is caused by mutations of LDL receptor or other protein that affects LDL receptor activity. Homozygous forms are rare, but are associated with rapidly progressive atherosclerosis leading to CVD and mortality in the first two decades of life. More commonly, heterozygous form is present with accelerated atherosclerosis and cardiovascular events before age of 50 years. These patients mostly have isolated elevation of LDL [19].

Familial combined hyperlipidemia is characterized by mixed dyslipidemia (LDL and triglycerides may be high or normal, HDL normal or reduced) with significant production of very low-density lipoprotein (VLDL) cholesterol and increased risk for CVD. It is less likely to be diagnosed in children, since significant elevations in fats may not occur until late adolescence, however apolipoprotein B levels may rise earlier and may be a better marker for this condition. In adults it is associated with features of metabolic syndrome and insulin resistance [19].

Rarely, severe hypertriglyceridemia may also be of genetic origin. Patients are likely to have a defect in lipoprotein lipase [19].

Some forms of secondary dyslipidemia (**Table 2**) are more frequent in children than in adults, and should be evaluated for [19].

Correction of secondary causes should normalize lipid levels, if there is no underlying genetic factor. Otherwise, the core management of dyslipidemia is lifestyle change with regular exercise, reduced screen time and diet. Dietary change should include total fat in less than 30% of daily caloric intake, with 8–10% saturated fat, avoidance of trans-fats and cholesterol intake less than 300 mg/day. This may be advanced to restriction of saturated fat less than 7% and cholesterol intake less than 200 mg/day if dyslipidemia persists. This level of restriction was found to be safe for growth and development. Water-soluble fiber and plant sterols may complement the diet. Patients with hypertriglyceridemia should also limit their sugar intake with replacement of simple sugars with complex carbohydrates and increase of omega-3 fatty acid intake [19, 23].

If lifestyle change over 6–12 months is unsuccessful, pharmacological treatment may be added. Statins were shown to be efficacious in children with familial hypercholesterolemia with a good safety profile. In children above 10 years of age,

Etiology subgroup	Possible underlying etiology
Endocrine/Metabolic	Diabetes - type 1, type 2 Hypothyroidism Polycystic ovarian syndrome Lipodystrophy Klinefelter syndrome Glycogen storage disease Gaucher disease Niemann-Pick disease
Cardiac	Kawasaki disease Orthotopic heart transplant
Rheumatological	Juvenile inflammatory arthritis Systemic lupus erythematosus
Gastrointestinal	Obstructive liver disease/other cholestatic conditions Alagille syndrome Biliary cirrhosis Hepatitis
Renal	Nephrotic syndrome Chronic renal disease Renal transplant
Medications/Exogenous	Glucocorticoids Isotretinoin Oral contraceptive therapy ß blockers Antipsychotics Alcohol

Table 2.
Causes of secondary dyslipidemia in children.

cholesterol absorption inhibitors may be added as adjunctive therapy. Bile acid sequestrants (cholestyramine, colestipol) also lower cholesterol level, but may have adverse gastrointestinal effects, such as gas, bloating, constipation and cramps, that limit their use and decrease compliance. Fibrates, niacin and orlistat lower triglyceride levels. For some genetic causes, novel treatment options are emerging, such as PCSK9 monoclonal antibody therapy [19, 23, 24].

5. Diabetes mellitus and insulin resistance

Diabetes is an additional cardiovascular risk factor that needs to be addressed in children. Historically, diabetes mellitus type 1 was considered of main importance in children. With increasing obesity, diabetes mellitus type 2 is becoming more prevalent [25]. Other etiologies, causing diabetes mellitus in children, are presented in **Table 3** [26].

Etiology subgroup	Possible underlying etiology
Type 1	Immune mediated Idiopathic
Type 2	
Other specific types	Genetic defects of ß-cell function Maturity onset diabetes of the young (MODY) Mitochondrial diabetes Genetic defects in insulin action Type a insulin resistance Leprechaunism Rabson-Mendenhall syndrome Lipoatrophic diabetes
Diseases of the exocrine pancreas	Cystic fibrosis Hemochromatosis Pancreatectomy
Endocrinopathies	Cushing syndrome Pheochromocytoma Hyperthyroidism
Medications or chemical induced	Glucocorticoids Diazoxide ß adrenergic agonists Pentamidine Nicotinic acid Interferon α Tacrolimus
Infections	Congenital rubella Cytomegalovirus
Uncommon forms of immune-mediated diabetes	"stiff-man" syndrome Anti-insulin receptor antibodies
Other genetic syndromes sometimes associated with diabetes	Down syndrome Turner syndrome Klinefelter syndrome Wolfram syndrome Friedreich ataxia Prader-Willi syndrome Bardet-Biedl syndrome Myotonic dystrophy

Table 3.
Causes of diabetes mellitus in children.

Regardless of the type of diabetes mellitus, hyperglycemia leads to impaired cardiovascular function, which was demonstrated in type 1 diabetes mellitus with impaired carotid artery structure and function, and decreased elastic properties of the aorta, already in children [27]. Diabetes mellitus is associated with a two-fold increase in the risk of CVD with a premature cardiovascular mortality and further risk increment when other cardiovascular risk factors coexist [28]. Early onset of diabetes mellitus further worsens cardiovascular risk [28].

Studies in the last decades indicate that insulin resistance is the predecessor of type 2 diabetes mellitus and has been associated with obesity, metabolic syndrome, hypertension and heart disease. It is defined as decreased tissue response to insulin and its cellular actions, commonly associated with obesity, however, not always, and not all obese have insulin resistance. Clinically, methods for insulin resistance measurement are scarce and, in many cases, limited to the research environment, however, one of the consequences of insulin resistance is chronic compensatory hyperinsulinemia, which can be demonstrated [29].

The diagnosis of both, diabetes mellitus and insulin resistance, is based on clinical symptoms, blood glucose monitoring, oral glucose tolerance test, and additional optional investigations, such as autoantibodies associated with diabetes or insulin levels [30]. In diabetes mellitus type 1 insulin therapy should be initiated immediately with recommendation of eventual insulin pump application in all small children, in patients with dawn phenomenon, severe hypoglycemia events or severe blood glucose fluctuations, glycated hemoglobin (HbA1c) values outside target range despite intensified conventional therapy, incipient microvascular or macrovascular secondary disease, limitations of the quality of life, in children with great fear of needles, pregnant adolescents and competitive athletes [30]. Treatment of type 2 diabetes mellitus and preceding insulin resistance is similar to treatment in adults. Weight loss and lifestyle change is the cornerstone of initial management. Patients may also be treated with oral agents, most appropriately starting with metformin, the only registered oral agent in children with diabetes mellitus type 2, and some may require administration of insulin to achieve glycemic control [31, 32].

6. Cardiovascular risk and kidney disease

The relationship between cardiovascular risk factors and chronic kidney disease is reciprocal: chronic kidney disease is a risk factor for CVD and cardiovascular damage accelerates kidney damage. Therefore, when we talk about vascular damage, we are really also talking about kidney damage and vice versa.

CVD is responsible for the majority of deaths in children with chronic kidney disease because of a high prevalence of traditional and uremia-related cardiovascular risk factors, with the highest risk in patients on dialysis. The cardiovascular alterations begin early in pediatric chronic kidney disease. Early markers of cardiac involvement, such as left ventricular hypertrophy and dysfunction, and early markers of atherosclerosis, such as increased carotid artery intima media thickness and increased arterial stiffness, are frequently present in children with chronic kidney disease [33, 34]. In children with early chronic kidney disease, before needing dialysis, modifiable cardiovascular risk factors should be identified and appropriate interventions should take place to decrease or delay premature CVD. Slowing down the progression of chronic kidney disease with avoidance of dialysis might be the best strategy to decrease cardiovascular risk [35].

7. Selected novel cardio-vascular risk factors

Diagnostic work-up should also include other cardiovascular risk factors that do not belong to the traditional ones that were described above. For example, urate is believed to be an independent indicator of arterial hypertension in children associated also with renal dysfunction [36]. Lipoprotein (a) is not associated with obesity, such as other lipoproteins, but is regarded as an independent cardiovascular risk factor and was found to be high in children with a family history of premature cardiovascular events [37]. Elevated levels of homocysteine were found in children with abdominal obesity [38], however a genetic hyperhomocysteinemia with mutations in methylenetetrahydrofolate reductase (MTHFR gene) was associated with stroke in children and in affected children with hyperhomocysteinemia and recurrent risk of stroke might be prevented with folate supplementation [39]. Vitamin D is frequently deficient in obese potentially leading to osteomalacia, and was additionally associated with insulin resistance and elevated blood pressure [40, 41]. Some studies even showed a higher risk of CVD and mortality when vitamin D was deficient, emphasizing the need for its supplementation [42].

To assess end-organ damage, kidney function, heart anatomy, and ocular background examination are commonly implemented, however, blood vessels, directly damaged by atherosclerosis, can be evaluated with intima media thickness and vessel elasticity evaluation. Intima media thickness is regarded as a subclinical indicator of atherosclerosis but has a lesser predictive value in children than in adults. There were several studies indicating an association between intima media thickness and obesity, familial hypercholesterolemia and hypertension in children, but sometimes associations were not clear cut and intra- and interoperable comparability raised doubts in the method [43]. Arterial stiffness can be commonly assessed with pulse wave velocity measurement that can be performed by several different methods, such as applanation tonometry. The higher the velocity of the pulse wave, the less compliant artery is expected, suggesting subclinical atherosclerosis. In children, several cardiovascular risk factors were associated with higher pulse wave velocity, however, the method is not in routine use [44].

8. Diagnostic work-up of cardiovascular risk factors in children

Cardiovascular complications, such as myocardial infarction and stroke, are rare in children, however, cardiovascular risk factors are increasing in prevalence, mostly due to worldwide increment of obesity. Preventive measures are most important in children and young adults, where the atherosclerotic process can be slowed down and possibly clinical manifestations of cardiovascular disease delayed [45].

Preventive measures can be individualized or population-based. The individualized approach includes active search of at-risk children during health check, who are more likely to develop premature CVD due to an underlying disease, inappropriate lifestyle or genetic disposition. Population-based approach includes interventions that affect the entire population aiming to lower cardiovascular risk in the whole population [45].

In pediatrics, we are most commonly involved in an individualized approach. Established recommendations in cardiovascular risk management in children involve two different goals: the prevention of risk-factor development and prevention of future CVD by effective management of identified risk factors. Therefore, several risk factors should be evaluated for, namely family history, diet, physical inactivity, tobacco exposure, blood pressure, lipid levels, overweight or obesity, diabetes mellitus, metabolic syndrome and perinatal factors [45].

	Investigations
Laboratory work-up	• Blood tests: complete blood count, electrolytes, kidney function and liver damage markers, lipidogram, apolipoprotein A1 and B, lipoprotein (a), urate, homocysteine, cystatin C, TSH, blood sugar, HbA1c, vitamin D • Urine tests: urinalysis, 24-hour urine sampling for proteinuria, albumin/creatinine in morning void sample • Optional investigations to exclude secondary causes
Imaging	• Abdominal ultrasound • Intima media thickness • Heart ultrasound • Ocular background examination • Optional investigations to exclude secondary causes
Functional diagnostics	• ECG • Ambulatory blood pressure measurement • Oral glucose tolerance test with insulin levels • Pulse wave velocity • Optional investigations to exclude secondary causes

Table 4.
Common investigations in children with cardiovascular risk; TSH—thyroid stimulating hormone, HbA1c—glycosylated hemoglobin, ECG—electrocardiogram.

The management of children with cardiovascular risk factors should be tailored to identify other possible cardiovascular risks, to evaluate end organ damage and to advise proper therapy. It starts with a good history with focus on family history and lifestyle. Next, clinical examination with anthropometric measurements with respect to percentile curves and blood pressure measurement should be performed. If blood pressure is elevated on multiple occasions, an ambulatory blood pressure measurement is recommended. Further work-up depends on history and examination and involves several laboratory, imaging and functional diagnostics, presented in **Table 4**.

In addition to above diagnostics, selected novel cardiovascular factors can be determined. Quite a few new diagnostic options to better define cardiovascular risk are on horizon, investigated in prospective studies, shortly presented in the next section.

9. Psychosocial aspect

Along with the management of classic cardiovascular risk factors, psychosocial aspects should also be evaluated. They can be partly responsible for disease development or can be a consequence of a chronic disease.

Early-life psychosocial factors that may influence cardiovascular health in adulthood include self-regulation (the ability to manage behavior, emotion, attention and social interactions), cognitive ability and aspects of home environment. They influence life-long health by facilitating education, problem solving, memory, communication, sense of control and ability to cope with stressful situations. Higher levels of psychosocial features were associated with greater likelihood of favorable cardiovascular state in adulthood with healthy levels of blood pressure, cholesterol, body mass index, cardiovascular-related medication status, smoking and blood sugar [46].

On the other hand, a chronic disease present in a child can have an important impact in a child's life and his or her family. Psychosocial issues are under-recognized, persist into adulthood and may impede optimal outcome. Children with chronic illness are at increased risk for mental health and adjustment problems. Child's adjustment depends mostly on the way the family copes with the child's condition. In young people, especially adolescents, underlying psychosocial issues can be suggested when new medical symptoms arise that cannot be explained by organic disease, when poor compliance to therapy is evident, when school refusal is present and when risky behavior involving excessive use of substances or excessive sexual behavior arises. These signs should alert the pediatrician to refer the patient to psychological treatment in time. Interventions are family-based, educational and are building on strengthening relationships and positive support [47].

Childhood obesity, a major contributor to CVD risk in modern society, can profoundly affect a child's social and emotional well-being and self-esteem. Obesity is associated with increased anxiety, body dissatisfaction and lower self-esteem. In obese, higher prevalence of eating disorder is present. In addition, obesity affects children's and adolescent's social and emotional health. Obese children are often bullied for their weight, excluded from activities, particularly physical, and face numerous negative stereotypes, discrimination and social marginalization, leading to further lower self-esteem, self-confidence, negative body image and negative effect to academic performance. The latter is in part due to chronic health-related conditions responsible for missing school [48].

10. Future perspectives

Despite numerous investigations and several cardiovascular risk factors evaluation, we still do not have a marker or investigation with prognostic value that would predict future CVD and premature cardiovascular events in children at risk. Several new biomarkers and investigations are emerging in research environment to assess cardiovascular risk, such as kidney injury molecule 1, adropin, salusin-α and -ß, uromodulin, markers of oxidative stress, along with functional diagnostics such as body composition measurement and elastography. Kidney injury molecule 1, a known marker for kidney tubular necrosis, was found elevated in overweight children [49]. Salusin-α and -ß are involved directly in the process of atherosclerosis with salusin-α slowing down and salusin-ß promoting atherosclerosis. In children, salusin-α correlated negatively with diastolic pressure [50, 51]. Adropin was discovered recently as a regulator of endothelial function among its several other physiological roles, such as angiogenesis, metabolism of glucose, fatty acids and dyslipidemia. Its role is protective and in overweight children lowered levels were found [52]. Uromodulin has an immunomodulatory role. In urine, it serves as a marker of kidney damage, however, in blood serum in elderly it was found to be a marker in CVD prognosis [53]. Children with diabetes had lower levels of serum uromodulin that correlated negatively with albuminuria [54]. Atherosclerosis, nowadays considered a chronic inflammatory process, is also being extensively researched through inflammatory markers and markers of oxidative stress, and some association with overweight in children has already been shown [55]. Very recently, microRNA is emerging as another possible diagnostic or therapeutic target that is being increasingly studied. Its postranslational function involves role in lipid metabolism, however, additional research, especially in children, is warranted [56], as for all other above mentioned biomarkers.

Along with fat mass evaluation, discussed in the second section, ultrasound and magnetic elastography are emerging as novel techniques for organ elasticity

determination. The use of ultrasound elastography opens up a new spectrum of ultrasound applications - its use has spread in liver and tumor stiffness evaluation, and several new indications are emerging in the research environment [57]. In the context of cardiovascular risk assessment, liver elasticity could be evaluated in obesity to assess the degree of steatosis or fibrosis without invasive liver biopsy [58]. Ultrasound elastography might also non-invasively assess elastic properties of the kidney aiming to quantify intrarenal fibrosis that could contribute to the overall assessment of renal function [59]. In children, liver elastography has been successfully performed, however, other areas remain a subject of research. The predictive value of elastography in the context of cardiovascular risk has yet to be determined.

Cardiovascular risk factors are strongly affected by environmental factors and unhealthy lifestyle choices. However, some susceptibility is inherited and related to the cumulative effect of many common genetic variants. With the progress of genetic diagnostics, made in recent years, there is also a place for the research of genetic susceptibility and the role of genetic markers and their possible implementation in clinical praxis. Genome-wide association studies have been successful in identifying some associations of single nucleotide polymorphisms for coronary artery disease. It has been shown that some of the manifestations of coronary heart disease, such as calcification, ectasia and main-stem stenosis, are more strongly inherited than others. The results of genome-wide association studies are believed to aid in individual risk prediction for cardiovascular risk and events development by molecular biological methods [60, 61].

11. Conclusions

Cardiovascular diseases are the main cause of morbidity and mortality in the world and several cardiovascular risk factors contribute to this fact already in childhood. With the obesity epidemic, risk is multiplying for next generations, with expectation of further increase in cardiovascular diseases. The prevention, or at least a delay, represents a challenge for pediatricians, because if treated early, cardiovascular complications may be potentially reversible. Interventions should be initiated as soon as possible to avoid the development of potentially untreatable disease.

Conflict of interest

The authors declare no conflict of interest.

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