Cardiovascular Complications Of Obesity

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Cardiovascular diseases (CVD) develop slowly over the life since fetal life and they are considered the main cause of death worldwide. In 2010 the American Heart Association defined a new concept of ideal cardiovascular health as the presence of both, ideal health behaviours (non-smoking, ideal BMI, physical activity and healthy diet) and ideal health factors (total cholesterol concentration, blood pressure and fasting glucose within the normal range)\(^1\). Childhood obesity is one of the most important factors involved in CVD development. Even with no accompanying comorbidities it is associated with cardiovascular system involvement and, additionally, is related to several CVD risk factors \(^2\). Impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, metabolic syndrome (MS), and vascular abnormalities may be present in overweight children and adolescents\(^2,3\). It was demonstrated that about 13% of obese youth suffer from hypertension and in 80% low HDL-cholesterol and in 10% high triglycerides (TG) levels are present \(^4\). There are also other, well known risk factors [Table 1], which are present in childhood. They could significantly modify the course of CVD caused by obesity and classic risk factors \(^5\).

**Table 1.** Genetic, environmental, and lifestyle risk factors of cardiovascular disease (CVD) in children and adolescents \(^5\).

<table>
<thead>
<tr>
<th>Fetal origins of CVD</th>
<th>1. Low birth weight</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2. High birth weight</td>
</tr>
<tr>
<td></td>
<td>3. Rapid catch-up growth of low-birth-weight newborns</td>
</tr>
<tr>
<td></td>
<td>4. Maternal obesity or excessive weight gain during pregnancy</td>
</tr>
<tr>
<td></td>
<td>5. Gestational diabetes</td>
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<tr>
<td></td>
<td>6. Maternal smoking during pregnancy</td>
</tr>
<tr>
<td></td>
<td>7. Maternal obesogenic, high-fat, high-salt diet during pregnancy</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td></td>
</tr>
<tr>
<td>Epigenetic deregulation of gene expression during fetal life</td>
<td></td>
</tr>
<tr>
<td>Ethnic predisposition</td>
<td>1. Asian, Afroamerican, Hispanic origin</td>
</tr>
<tr>
<td>Family history of premature CVD</td>
<td></td>
</tr>
<tr>
<td>Growth pattern</td>
<td>1. Rapid catch-up growth of low birth weight</td>
</tr>
<tr>
<td></td>
<td>2. Childhood obesity</td>
</tr>
<tr>
<td>Poor socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>Lifestyle</td>
<td>1. Bad dietary habits</td>
</tr>
<tr>
<td></td>
<td>2. Low physical activity</td>
</tr>
<tr>
<td></td>
<td>3. Tobacco smoking</td>
</tr>
<tr>
<td>Environmental factors</td>
<td>1. Air pollution</td>
</tr>
<tr>
<td></td>
<td>2. Secondary tobacco smoking</td>
</tr>
</tbody>
</table>
The appearance of risk factors in childhood is not connected with increased morbidity and mortality from CVD at the young age, but it may predict an increased risk of CVD in adult life. Bibbins-Domingo et al. in 2007 estimated that in United States, the number of additional cardiovascular events attributable to excess weight in adolescence would reach more than 100,000 excess cases per year by the year 2035. It was found that the risk of any CV event, a nonfatal or fatal, among adults is positively associated with BMI at 7 to 13 years of age for boys and 10 to 13 years of age for girls and the risk increased across the entire BMI distribution. Baker et al. found that in comparison with an average-size 13-year-old boy, a boy of the same age and height weighing 11.2 kg more had a 33% higher risk of having a CVD event in adulthood. However, for obese children younger than 7 years, the data are inconsistent and some researchers did not find any relationship between excessive body weight and future CV risk.

Four big prospective cohort studies, the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study, demonstrated that childhood obesity, MS and poorly controlled classic CVD risk factors, contribute to progression of coronary artery atherosclerosis and carotid artery calcification in adulthood. Very clear evidence for the association between childhood obesity and early risk of CVD is the presence of fatty streaks and fibrous plaques found on autopsy studies of adolescents. Extent of atherosclerotic lesions in the coronary vessels increased markedly in young people with high values of BMI and with other CVD risk factors. Moreover, Shah et al. demonstrated that adolescents’ and young adults’ obesity is related to increased left ventricle mass and geometric changes consistent with cardiac remodelling, which can predict an increased incidence of clinical events attributable to CVD. It is worth mentioning that during childhood, markers of CVD risk have a complex profile, corresponding also to body growth and not only fat accumulation.

It is still a matter of discussion if excessive body weight or rather tracking of BMI from childhood to adulthood plays major role as an independent CVD risk factor. Overweight or obese children who were obese also as adults had increased risk of T2DM, hypertension, dyslipidemia, and carotid artery atherosclerosis. Juonala et al. found that obese children that were not obese as adults had similar CVD risk to those that maintained a normal BMI from childhood to adulthood. On the other hand, Tirosh et al. demonstrated that adults who were obese as youth, even when controlling for adult BMI, had a higher risk not only of cardiac events but also of an early mortality. Most probably both factors, degree and duration of childhood and adolescent obesity, are important for determining cardiovascular health in the future.

**Cvd Markers In Childhood**

There are some early atherosclerosis markers which indicate preclinical CVD and can be found in obese children and adolescents. Vascular abnormalities characteristic for atherosclerosis are present even in young children. *Fatty streaks & fibrous plaques* in the aorta, although reversible, arise at around 3 years of age and may involve up to 15% of the aorta. In the autopsy studies fatty streaks were present in the coronary arteries of adolescents between 10 and 14 years of age. Their formation is connected with high concentration of LDL-cholesterol and proinflammatory state. Many risk factors such as dyslipidemia, diabetes mellitus, smoking, etc. provoke enzymatic and non-enzymatic formation of modified LDLs, which enter the cell through various scavenger receptors, leading to foam cell formation.
and following plaque development.

The next early marker of atherosclerosis, related to CVD risk in adults is increased arterial stiffness. Its characteristic feature, central pulse wave velocity (PWV), which is assessed by tonometry is highly correlated with CVD and predictive of CVD morbidity. Increased arterial stiffness is present already in obese children. Dangardt et al. found that over the course of 5 years, arterial stiffness assessed by PWV increased by 25% in the obese adolescents as compared to 3% in the lean subjects. In addition, the increase in arterial stiffness was positively associated with BMI z-score at baseline. Vascular stiffness is not only increased in the central arteries but also in pulmonary artery, what can be an early marker of pulmonary hypertension.

The vascular endothelium plays a key role in the progression of atherosclerosis, development of coronary artery disease, hypertension and congestive heart failure. Adipose tissue is extremely important in the development of endothelial dysfunction in obese patient. Stimulation of the proinflammatory state, insulin resistance and high production of free fatty acids are the most important factors involved in the mechanism leading to endothelium damage. Flow mediated-dilatation (FMD) assessed by noninvasive ultrasound examination is an early clinical indicator of atherosclerosis and endothelium damage. Several studies have reported that children with obesity have lower FMD compared to children with healthy weight. Moreover, Ciccone et al. showed that BMI in overweight and obese children correlates with carotid intima media thickness (IMT) as well as with FMD.

Arterial IMT is a noninvasive measure of subclinical atherosclerosis and appears to be a useful tool to identify potential risk in young people. Carotid IMT has been shown to be predictive of stroke and myocardial infarction in adults. Early weight gain in infants and toddlers is associated not only with increased risk of overweight and obesity, but also with higher arterial IMT in later childhood. High adolescent BMI was associated with higher rates of both coronary artery calcification and carotid IMT. Using IMT, Le et al. tried to assess the so called vascular age. They found that 75% of obese children and adolescent with atherosclerosis-promoting risk factors had advanced vascular age, similar to what would be expected for 45-year-old adult.

In obese children and adolescents some impairment of cardiac structure and function can be found. Left atrial and left ventricle (LV) dimension as well as LV mass are significantly greater in children with obesity compared to children with normal BMI. These changes might be an early consequence of increased blood volume and hyperkinetic circulation in the obese state, in which the excessive fat mass constitutes an ‘extra organ’, demanding augmented cardiac output. Also geometric changes consistent with cardiac remodelling are present in obese youth. LV hypertrophy is potentiated by obesity and has been demonstrated to predict an increased incidence of clinical events, including death caused by CVD. Additionally, there is an evidence that childhood adiposity can affect systolic and diastolic function of the heart, both at rest and during exercise. Moreover, the duration of obesity seems to be the major factor that determines the likelihood of developing systolic dysfunction and heart failure. Strain and strain rate, assessed by tissue Doppler, are related to heart fibre shortening and the speed of fibre shortening, respectively. These parameters are important in assessing subclinical myocardial dysfunction. In obese children reduction of left and right ventricle strain and strain rate, the optimal descriptors of cardiac contraction and relaxation, were found by di Selvo et al.
Increased *epicardial fat* has been also reported in overweight children. It was correlated positively with LV mass. Epicardial adipose tissue is deposited between the pericardium and outer wall of the myocardium and it is suggested to be a CV risk predictor. In adults it correlates with insulin resistance, coronary artery disease and with preclinical markers of atherosclerosis, carotid IMT and arterial stiffness. In obese children epicardial fat is related to BMI, carotid IMT, left atrium volume, LV mass, and PWV. It seems that epicardial fat measurement could be a simple and noninvasive screening tool to predict cardiometabolic dysfunction in obese children.

**Cardiovascular Risk Factors**

**Hypertension**

Blood pressure is a continuous variable that is positively correlated with CV risk across the entire blood pressure range. It tracks with age and if elevated at a young age predicts essential hypertension in adulthood. Persistently elevated blood pressure from childhood to adulthood increases the risk of carotid atherosclerosis. Hypertension in childhood is defined by systolic or/and diastolic blood pressure at or above 95 percentile for age, sex and height [Table 2]. There is very strict association between hypertension and obesity in childhood. It is estimated that 37% of childhood hypertension could be attributed to excessive body weight. The risk of hypertension is 2.5 – 3.7 times higher in obese children compared to non-obese ones. It is believed that the presence of excessive weight appears to be one of the most important factors related to hypertension in children and adolescents worldwide. In prepubertal girls every 1-unit increase of BMI z-score is associated with increase in systolic blood pressure of about 9 mmHg, in adolescent boys – with 2.4 mmHg. Obese adolescents had an average of 7.6 mmHg higher systolic blood pressure that of normal weight peers. Moreover, the presence of obesity is positively correlated with the occurrence of prehypertension in children and adolescents, and this combination increases the risk of developing adult hypertension. Obese children have tenfold greater risk of hypertension as young adults. There is evidence that risk of raised blood pressure is highest in those who are at the lower end of the BMI scale in childhood and overweight in adulthood.
Table 2. Recommended lipid and blood pressure levels in children and adolescents.\(^ {46}\)

<table>
<thead>
<tr>
<th></th>
<th>Acceptable</th>
<th>Borderline</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol [mg/dl]</strong></td>
<td>&lt;170</td>
<td>170-199</td>
<td>≥200</td>
</tr>
<tr>
<td><strong>Triglycerides [mg/dl]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9 y</td>
<td>&lt;75</td>
<td>75-99</td>
<td>≥100</td>
</tr>
<tr>
<td>10-19y</td>
<td>&lt;90</td>
<td>90-129</td>
<td>≥130</td>
</tr>
<tr>
<td><strong>HDL-cholesterol [mg/dl]</strong></td>
<td>≥45</td>
<td>40-45</td>
<td>-</td>
</tr>
<tr>
<td><strong>Non-HDL cholesterol [mg/dl]</strong></td>
<td>&lt;120</td>
<td>120-144</td>
<td>≥145</td>
</tr>
<tr>
<td><strong>LDL-cholesterol [mg/dl]</strong></td>
<td>&lt;110</td>
<td>110-129</td>
<td>≥130</td>
</tr>
<tr>
<td><strong>Blood pressure (systolic or diastolic) [mmHg]</strong></td>
<td>&lt; 90(^{th}) percentile</td>
<td>90(^{th})-95(^{th}) percentile</td>
<td>&gt;95(^{th}) percentile</td>
</tr>
</tbody>
</table>


There are many mechanisms related to obesity that could contribute to the development of hypertension. Obesity-induced hypertension may be mediated in part by sympathetic nervous system hyperactivity, which leads to increased renal sodium retention and increased systemic vascular resistance.\(^ {29,33}\) Additionally, the evidence of reduced vagal or parasympathetic activity, resulting in decreased heart rate variability, which is related to CVD development and mortality, were found in obese children.\(^ {17}\)

Moreover, diminished baroreflex sensitivity, important for regulating blood pressure, has also been reported.\(^ {34}\) In spite of sympathetic nervous system disturbances, increased systemic vascular resistance can occur directly in obese individuals through vascular fibrosis and lipid deposition.\(^ {33}\) Additionally plasma renin activity, angiotensinogen, angiotensin II and aldosterone levels are significantly increased in obese subjects. The severity of obesity has been shown to positively correlate with plasma renin activity.\(^ {22}\)

The key role in all above mentioned mechanisms, play insulin resistance, dyslipidaemia, as well as proinflammatory cytokines that may promote an altered vascular function and consequently hypertension.\(^ {33,35}\)

**Dyslipidaemia**

Lipid disturbances are the most common consequence of childhood obesity and are present in as many as 43% of obese adolescents. The lipid pattern associated with obesity is known as combined dyslipidaemia and is characterized by moderate to severe elevation in TG and non–HDL cholesterol, decreased HDL cholesterol, and mild to moderate elevation in total (TC) and LDL cholesterol [Table 2].\(^ {35}\) Dyslipidaemia is related significantly to insulin resistance as the latter is enhancing hepatic delivery of non-esterified free fatty acids for TG production and sequestration into triglyceride-rich lipoproteins. TGs are deposited in the vessel wall and initiate the process of LDL accumulation. They are strongly associated with the risk of developing atherosclerotic disease.\(^ {15}\) LDL, very low-density lipoprotein (VLDL), and lipoprotein-a are the primary apolipoprotein-B containing lipoproteins implicated in the formation of atherosclerotic lesions.\(^ {22}\) HDL has been thought to be protective though its ability to prevent oxidation of LDL.
promotes reverse cholesterol transport leading to decreased macrophage uptake of oxidated lipids and foam cells forming which are involved in atherosclerotic plaque formation.

Lipid disturbances that begin during childhood, tend to be maintained through development. Several studies describe a direct relationship between TC levels in children and heart disease in adults. In the study of Rodriguez et al. 15 cholesterol levels in adolescence correlated with 87% of deaths due to heart disease in adulthood and showed that high levels of cholesterol are accompanied by a high mortality rate. Combined dyslipidaemia in childhood has been shown to independently predict increased carotid IMT at 21-year follow-up, and coronary disease events in young adult life 36. Elevated adolescence LDL-cholesterol, as well as systolic blood pressure are independent predictors of adulthood coronary artery calcium 37. It is estimated that each 1% reduction in TC results in a decrease of 2% in the occurrence of coronary artery disease 15.

Type 2 Diabetes And Glucose Metabolism Disturbances

Insulin resistance in obese children is the initial metabolic abnormality in the pathway toward glucose intolerance and T2DM [Table 3]. Persistent overweight through childhood, adolescence and adulthood is associated with 12-fold increase in risk of T2DM 38. It was hypothesized that disease progression, in which overweight contributes by increasing insulin resistance, is causing the loss of beta cells over time, eventually leading to T2DM 39. Impaired glucose tolerance is present in 25% of obese children and 21% of obese adolescents, moreover silent T2DM can be found in 4% of obese adolescents 40.

Both insulin resistance and diabetes increase the cardiovascular risk. Insulin resistance determinates arterial stiffness, independently of obesity and other additional CVD risk factors, leading to increase blood pressure 22. Many complications of T2DM are related to the diabetes duration. Therefore, when T2DM develops in childhood, the early onset predicts early complications such as renal failure and cardiovascular events. Compared to an average 20-year-old without T2DM, a 20-year-old with T2DM has on average 15.5 fewer years of life expectancy, mainly caused by micro- and macrovascular complication of the disease 41. Moreover, the risk of complication, as well as the risk of mortality from T2DM-related comorbidity increases with age. Increased glucose level at the age of 15 years is a significant risk factor for coronary artery calcium. Loria et al. 42 found 3-fold increased odds ratio of having coronary artery calcium for those subjects with glucose >110 mg/dl. Hyperglycemia leads to increased glycosylation of LDL thus worsening atherogenicity of the protein 22. Important is that the improvement of the glucose control leads to decrease of micro and macrovascular complications of diabetes, including atherosclerosis.

See also chapter “Insulin resistance and the risk of diabetes”
Table 3. Classification of glucose metabolism disturbances in children and adolescents.

<table>
<thead>
<tr>
<th></th>
<th>Fasting glucose [mg/dl]</th>
<th>120’ OGTT glucose [mg/dl]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desires</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>100-125</td>
<td></td>
</tr>
<tr>
<td>Impaired Glucose Tolerance</td>
<td>-</td>
<td>140-199</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥126</td>
<td>≥200</td>
</tr>
</tbody>
</table>

Clustering Of The Risk Factors – Metabolic Syndrome

The MS is an insulin resistance-related set of clinical characteristics known to increase the risk of CVD, T2DM, and mortality in adults [Table 4] ²³. It is a combination of risk factors, including increased waist circumference, hypertension, hypertriglyceridemia, hyperglycaemia and low HDL-cholesterol ²³. The insulin resistance is the leading cause of the hemodynamic and metabolic disorders in MS ¹⁵,43. It is estimated that 30-50% of overweight children meet the criteria of MS ⁴⁴. In the Young Finns study, youth obesity was the strongest risk factor for MS and was associated with the development of adult MS, independent of other risk factors ⁴⁵. MS in childhood is associated with a 1.5-fold increase in overall mortality and 2.5-fold increase in cardiovascular mortality in adults ¹⁵. The individuals with MS in youth and adulthood had 3.4-times bigger risk of high IMT compared with those that did not have MS at either time-point ⁴⁵.

Table 4. Metabolic syndrome criteria in children and adolescence ¹⁵.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
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<tbody>
<tr>
<td></td>
<td>6-10 y</td>
</tr>
<tr>
<td>Adiposity</td>
<td>WC&gt;90th percentile</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td>Fasting glucose &gt; 100 mg/dl</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>No defined cut off value for the diagnosis of metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>TG&gt;150mg/dl or HDL&lt;40 mg/dl or taking antilipidemic drug</td>
</tr>
<tr>
<td></td>
<td>TG&gt;150mg/dl or HDL&lt;40 mg/dl for boys and HDL&lt;50 mg/dl for girls or taking antilipidemic drug</td>
</tr>
<tr>
<td></td>
<td>SBP&gt;130 or DBP &gt;85 mmHg or taking antihypertensive drug</td>
</tr>
<tr>
<td>hypertension</td>
<td>SBP&gt;130 or DBP &gt;85 mmHg or taking antihypertensive drug</td>
</tr>
</tbody>
</table>

WC – waist circumference, TG – triglycerides, SBP – systolic blood pressure, DBP – diastolic blood pressure
Most of the early atherogenic changes in cardiovascular system present in obese children and adolescents are highly reversible at that stage. Although the manifestation of coronary heart disease occurs in adulthood, detecting risk factors during childhood is crucial for establishing a prognosis and preventing damage of the target organs in adults. The recommendations of clinical-practise management of CVD risk in children and adolescents are very well and widely established in “Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report” published in Pediatrics in 2011 year. Clinical intervention to prevent CVD should be taken up in all cases in all possible ways. The lifestyle, diet and exercise intervention, as well as more aggressive approaches such as pharmacotherapy and bariatric surgery in morbidly obese patients with serious complication are effective in improvement of cardiovascular morphology and function. It was found that obese children who were not obese as adults had similar CVD risk to those that maintained a normal BMI from childhood to adulthood. Magnusson et al. showed that youth with MS are at increased risk of adult high IMT and T2DM, however they also found that the resolution of MS components can, to some extent, normalize this risk to the normal level.
References:


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Dr Agnieszka Zachurzok graduated from Medical University of Silesia in 2002 and in 2003 she also graduated from the one-year course of molecular biology at the Jagiellonian University in Krakow. Since 2003 she has been working at the Department of Paediatrics, Endocrinology and Diabetes of the Medical University of Silesia. She participated in the European Society for Paediatric Endocrinology (ESPE) Winter School in Vilnius, Lithuania in 2004 and the ESPE Summer School in Sychrov, Czech Republic in 2010. In 2011 dr Zachurzok became a specialist in paediatrics, and started specialization in endocrine diseases. In 2004 she received the Ph.D. degree for a thesis: “Ovarian hyperandrogenism in adolescent girls with menstrual disorders”.

She is an assistant professor at the Department of Paediatrics, Endocrinology and Diabetes, Medical University of Silesia, Katowice, Poland, involved in clinical work, research and teaching. She is specially interested in thyroid diseases, obesity, metabolic syndrome and polycystic ovary syndrome. She was a partner in EU project “BOYS AND GIRLS”. Dr Zachurzok is a co-author of 26 papers in paediatrics and paediatric endocrinology published in peer-reviewed medical journals, her current IF is 10.5.

Dr Zachurzok is also involved in Outpatient Clinic for Obese Children and Adolescent dealing with a problem of obesity and its complication in everyday work. She is a member of Polish Endocrine Society and Polish Society of Paediatric Endocrinology and Diabetes. Since 2013 she is an active member of European Society of Endocrinology.
Prof. Ewa Malecka-Tendera has been involved in the field of paediatric endocrinology since 1976. In 1983 she completed six-month endocrinology training at the Vanderbilt University in Nashville (USA). She received Board certification in Endocrinology in 1996 and in Diabetes in 2011. In 2001 she received the scientific title and a position of full professor. Currently she works as Head of the Department of Paediatrics, Paediatric Endocrinology and Diabetes at the Medical University of Silesia. This department is EASO accredited Collaborating Centre for Obesity Management (COM).

Since 1993 she is a member of Polish Society for Paediatric Endocrinology. From 2005 to 2009 has been serving in the capacity of President of this Society. She is a member of ESPE since 1996 and she was appointed its POC member. She was also a POC member of EFES/ECE in Gothenburg, Istanbul and Glasgow, of the European Congress of Obesity in Geneva and ICE in Rio de Janeiro. She was an invited speaker of symposia, MTE and Pro and Cons sessions at several international meetings and workshops and was also a lecturer at ESE Postgraduate Training Courses in Clinical Endocrinology. In 2010 she was nominated a Jury Member of EJE prize.

Prof. Ewa Malecka-Tendera is also active in the field of childhood obesity. Since 1992 has been a member of the European Childhood Obesity Group (ECOG). Between 1997 and 2003 she was a Scientific Advisor of the board of ECOG. She was a partner in EU project “PERISCOPO” and “BOYS AND GIRLS”. She was the founding fellow of SCOPE and EMA expert on Obesity in Children.

She published more than 200 papers in international and Polish peer-reviewed journals and several book chapters on paediatric endocrine disorders as well as childhood and adolescent obesity prevalence, complications and management. Her current IF is around 96 with Hirsch Index 9.
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