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Lipid disorders in children – an underestimated problem

Zaburzenia lipidowe u dzieci – niedoszacowany problem

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Lipid metabolism disorders (dyslipidemias) are a heterogenic group of diseases that may occur at any age, and may be transient or last throughout life. They are one of the most common pathologies in the pediatric population. In the United States, approximately 20% of children (age 6 to 19 years) have abnormal levels of at least one lipid parameter value [1]. A similar frequency was found in the German population [2]. In adults, dyslipidemia is an established risk factor for cardiovascular disease (CVD). Because dyslipidemia often begins in childhood and adolescence, identifying children with dyslipidemia and successfully improving their lipid profile may reduce their risk of accelerated atherosclerosis and premature CVD [3]. Scientific evidence confirmed the relationship between hyperlipidemia at an early age and unfavorable changes in morphology of arterial intima layer which support the hypothesis that atherosclerosis has an early onset, being a chronic and progressive process [4, 5]. There are many factors affecting lipid metabolism, including genetic background, external factors, and a combination of these. The basic classification is based on the causes of the disorders and distinguishes the following: 1. primary dyslipidemias, that are a heterogeneous group of diseases of mono, or polygenic etiology, and 2. secondary dyslipidemias resulting from the association of risk factors with external factors or other pathologies [6]. Subdivision can also be according to biochemical changes as hypercholesterolemia (increased total cholesterol – TC and low-density lipoprotein cholesterol [LDL-C] levels), hypertriglyceridemia (elevated triglycerides – TG), low isolated levels of high-density lipoprotein [HDL-C] cholesterol, and lastly, simultaneously increased TC and TG associated with low levels of HDL-C (mixed or combined) [7]. Dyslipidemia often appears as a synonym for hyperlipidemia however, hypolipidemias such as abetalipoproteinemia, familial hypobetalipoproteinemia, or sterol synthesis defects should also be considered [6]. There are 25 forms of monogenic lipid disorders described in the literature [8]. The most common monogenic conditions include familial hypercholesterolemia (FH) caused by hepatic LDL-receptor dysfunction (approximately 85–90% of patients), changes in the apolipoprotein B protein receptor on the low-density lipoprotein particle surfaces (apolipoprotein B deficit), or a gain in the proprotein convertase subtilisin/kexin type 9 function, which is involved in LDL-receptor degradation [9]. Homozygous forms are rare but present at an early age in a more severe form (overt CVD in the first–second decade of life) than heterozygous forms, illustrating a broad phenotypic spectrum [6, 10]. It is estimated, that only 5% of patients with FH in Poland are aware of their condition [11, 12]. Some patients may have a clinical phenotype similar to that of FH but without a single mutation of sufficient pathogenicity to produce it. Such patients probably have multiple gene variants, each of which makes a small independent contribution. These patients are considered to have polygenic hypercholesterolemia [13]. Regardless, the risk of early CVD is significant in both. The second most frequent genetically determined dyslipidemia is familial hypertriglyceridemia [10]. It is caused by disorders in chylomicrons or very-low-density lipoproteins (VLDL) metabolism. The most frequent causes dysfunction of lipoprotein lipase (95%, despite autosomal dominant transmission, a clear genetic basis is unavailable), or rarely mutations in *APOC2*, *LMF1*, *GPIHBP1*, and *APOA5* genes [6]. It is characterized by increased TG levels in fasting (> 1000 mg/dl), that may cause acute pancreatitis, without atherosclerosis association or increased cardiovascular risk [14]. The rare form of primary dyslipidemia is sitosterolemia caused by excessive plant sterol absorption at the intestine. The phenotypic spectrum ranges from almost asymptomatic individuals to severe elevated TC, development of xanthomas, premature atherosclerosis, hemolytic anemia, and macrothrombocytopenia. It is caused by biallelic mutations in either *ABCG5* or *ABCG8* genes, which encode

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the sterol efflux transporters [15]. The deficit of hepatic lipase that hydrolyzes TG and phospholipids in VLDL and intermediate-density lipoprotein remnants prevent their conversion to LDL-C causes an increased TC, HDL-C, and TG from adolescence [16]. The secondary causes include specific diseases and conditions that are associated with dyslipidemia. Currently, the main cause is an excessive adipose tissue mass and its pathological metabolic activity. In some cases it may be also enhanced by genetic predisposition. In an analysis of the United States National Health and Nutrition Examination Survey (NHANES) data from 1996 to 2006, the likelihood of abnormal lipid values was higher in adolescents with greater body mass index (BMI). The prevalence among youths who were normal weight, overweight (BMI 85th to 95th percentile), and obese (BMI > 95th percentile) was 14%, 22%, and 43%, respectively [17]. The main common biochemical markers are elevated levels of TG and low HDL-C, often associated with increased activity of liver aminotransferases [18]. Other secondary dyslipidemias include disease or drug related disorders. For example nephrotic syndrome, malnutrition (anorexia nervosa), cholestasis, and the following drugs: progesterone, thiazide diuretics, carbamazepine, cyclosporine or mTOR inhibitors may cause hypercholesterolemia [6, 19]. Type 2 diabetes, kidney failure, sepsis, stress, Cushing's syndrome, hepatitis, human immunodeficiency viral infection, and the following drugs: protease inhibitors, anabolic corticosteroids, β-blockers, estrogen, and thiazide diuretics are causes of hypertriglyceridemia [6]. Low HDL-C levels are associated with smoking, physical inactivity, obesity, type 2 diabetes, malnutrition, steroids, and β-blockers use [6]. The diagnosis of dyslipidemia is based on abnormal blood cholesterol, lipoprotein and/or TG test results. In practice, this is difficult in children and adolescents, because the parameters values may change with age. Interpretation of cholesterol and lipoprotein determinations in the first 2 years of life is particularly difficult because serum TC and LDL-C levels are lower during intrauterine life and shortly after birth, but increase rapidly during the first week of life, and then gradually up to 2 years of age, then they remain relatively constant until adolescence, and then decrease, before rising in the late teenage years [10, 20–22]. Lipid levels are also affected by gender and ethnicity. For example males experience a decrease in HDL-C level during late puberty, while in females it remains stable until menopause [7, 13]. African American children have higher TC and HDL-C levels and lower TG levels compared with other racial/ethnic groups [13]. Therefore, lipid abnormalities in the pediatric age group should be identified based on the percentile thresholds [23]. Apart from the difficulties mentioned above, it is worth noting, that contrary to adults, proposed cutoff points for children have not been validated as accurate predictors for accelerated atherosclerosis or CVD events. Because most lipid disorders in children are asymptomatic, their diagnosis is most often based only on blood tests. There are two approaches to the diagnosis of lipid disorders: universal screening strategy or directed to the family or individual risk factors in asymptomatic patients. Taking into account the risks associated with the under detection of lipid disorders in childhood, but also all the above mentioned limitations of diagnostic methods, most experts currently support selective screening as the best diagnostic method. On the other hand, taking into account the low effectiveness of screening tests in adults (e.g. currently in Poland live about 20 million people with hypercholesterolemia, and the vast majority of them is not diagnosed), universal screening tests in children / adolescents can be seriously considered. [11, 12]. Selective screening should be performed on children/adolescents over 2 years old with family or individual risk factors (overweight/obesity, hypertension, smoking, sedentary life, or diabetes as soon as these factors are identified and regularly while present with 2 or 3 years interval) [6, 10]. Screening can be at fast or postprandial (TG level is higher postprandial) but must be confirmed in two fasting samples if altered. The average between these two values can be used for diagnostic and therapeutic purposes [7, 10, 24]. In all cases of dyslipidemias lifestyle changes are recommended, with a particular incidence of dietary treatment and increase of physical activity, and avoiding smoking [7]. In hypercholesterolemia the dietary intervention may include supplementation with stanols and plant sterols, substances structurally similar to cholesterol that inhibit their intestinal absorption. Supplemented commercial products have variable concentrations and can be used as co-adjuvants in lowering LDL-C (approximately 8% reduced TC) [25]. As demonstrated by Grabarczyk *et al*. in a recently published paper in *Pediatric Endocrinology Diabetes and Metabolism* 2022; 28 (2), correctly selected dietary supplements may be an alternative to statins with an equally effective effect in selected pediatric patients [26]. Dietary restrictions of hypercholesterolemia are not indicated below 2 years of age due to the increased need for dietary fats critical for the growth and development of the nervous system [25]. In hypertriglyceridemia, the initial dietary approach includes decreased sugar and saturated fat consumption, and increase of fish intake (rich in ω-3) [25]. The pharmacological options are several and must be selected according to the lipid profile and risk-benefit. It should be considered according to CVD risk stratification. Evidence establishing the long-term effectiveness of lipid-lowering interventions in children comes largely from studies in children with FH, a group at high risk for morbidity and early mortality. Statins that inhibit the reductase of 3-hydroxy-3-methylglutaryl- coenzyme-A, an enzyme that limits endogenous cholesterol synthesis with decreased intracellular cholesterol content and increased LDL-C clearance, have been the predominate agent utilized in clinical practice. Therapy with statins in children with FH decelerates the atherosclerosis process, as assessed by subclinical vascular findings (e.g, carotid intima-media thickness). However long-term outcome data on cardiovascular morbidity and mortality are not available for the general pediatric population. Despite that, current studies suggest that for the most beneficial effect statin treatment it should be started in childhood. Delay of the treatment can cause future CVD development. There is growing scientific evidence that statin therapy in pediatric patients is safe and effective [7, 26, 27]. Statin therapy may be initiated in children ≥ 10 years of age (except for children with FH, in whom the Forum of Lipid Experts in Poland recommends the use of

statins > 8 years of age (accumulating data support lowering of this age even to 6 years), and in children with homozygous FH < 8 years of age with LDL-C concentration > 500 mg/dl (12.9 mmol/l)) [10]. Cholesterol absorption inhibitors (ezetimibe), that inhibit intestinal cholesterol absorption from plant sterols, can be used from 10 years of age in children with FH and/or high-risk factors for premature CVD, who do not reach therapeutic goals with the optimized statin dose [14, 28]. In the most severe forms of homozygous FH, that usually poorly respond to standard treatment options, lipoprotein apheresis is an additional option for these patients; however, its effect on LDL-C concentrations is temporary and have to be repeated every 1–2 weeks [28]. Moreover, as noted by the authors of a recent study in *Pediatric Endocrinology Diabetes and Metabolism* (Grabarczyk *et al*. 2022; 28 (2)), in children with dyslipidemia, regardless of its background, statin therapy is the most effective in lowering LDL-C [26]. In recent years novel lipid-lowering drugs have been implemented. Currently, they are approved for patients with severe familial hypercholesterolemia. The possibilities of their use in children are currently limited and require further research [6, 28]. In 2021, the Food and Drug Administration (FDA) in United States, and the European Medicine Agency (EMA) approved evinacumab (fully humanized anti- Angiopoietin-like protein 3 antibody) as an add-on therapy for patients over 12 years of age with homozygous FH [29]. In 2021 and 2022 FDA and the EMA respectively approved evolocumab (human monoclonal antibody that inhibits PCSK9) for children above 10 years of age with primary homozygous FH [30]. Recently Ziółkowska *et al*. presented a detailed, current description of the pharmacotherapy currently used in FH, as well as the drugs undergoing suitability assessment, in the paper published in *Pediatric Endocrinology Diabetes and Metabolism* 2022; 28 (2) [31]. In familial hypertriglyceridemia drugs are less effective than low-fat diet. Fibrates, that are agonists of nuclear PPAR- receptors and favor TG and VLDL degradation, are only indicated in children with severe hypertriglyceridemia (> 500 mg/dl) or at risk of pancreatitis, who are unresponsive to dietary measures [14]. In combined hyperlipidemia associated with excessive body mass, the treatment should be concentrated on healthy habits implementation, that involves greater fruit and vegetable consumption, adequate water consumption, and daily physical activity, coupled with reduced consumption of sugary foods and drinks [25]. Lipid disorders in children are underdiagnosed and underestimated. There is still no direct evidence that their treatment reduces adult CVD mortality. But based on the indirect evidence there is a common belief that treatment should be started in childhood, and that early diagnosis and treatment may have long-term benefits.

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