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Children and adolescents' obesity is the 21st century health problem

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Abstract

The article presents a literature review which devotes to one of the major issues of healthcare today — obesity in children and adolescents. The consequences of childhood obesity, methods of determination and pathophysiology of obesity are described in detail. It was considered the influence of genetic factors in the formation of obesity, the effect of intestinal microbiota in the pathogenesis of obesity. The literature search was carried out in the databases of NCBI, PubMed, PubMed Central, eLIBRARY.ru, etc. Obesity in children and adolescents is one of the most important issues for people from most countries in today's world. Worldwide, the prevalence of this pathology has increased over the past three decades. Obesity in children and adolescents is a complex, multifactorial disease in which genetic and non-genetic factors can be identified. Although the vast majority of childhood obesity incidents are exogenous, a small proportion may have endogenous causes. Currently, particular importance is attached to the study of hereditary predictors of obesity and its main complications. Being a complex and inherited trait (disease), obesity is a consequence of the interaction of genetic predisposition, epigenetics, metagenomics, and the environment. Also, recent experimental and clinical data show the importance of intestinal microbiota, which can cause overweight and obesity in some patients. Molecular genetic studies have confirmed changes in intestinal biocenosis with developing obesity in children and adolescents. Obesity, which began in childhood, causes short-term and long-term adverse effects on physical and psychosocial health and largely becomes a risk factor for the development of various metabolic disorders and cardiovascular pathology. Understanding the multifactorial mechanisms involved in the formation of obesity in children and adolescents provides opportunities for the early prevention of obesity and its complications.

Keywords: review, obesity in children and adolescents, metabolic syndrome, genetics, microbiota.

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Obesity, defined by the World Health Organization as the abnormal or excessive accumulation of fat, which represents a health hazard, is a global disease with potentially devastating consequences [1].

Over the past few decades, there has been a tendency towards a rapid increase in the number of obese children and adolescents worldwide [2]. The number of obese children and adolescents aged 5 to 19 years increased from 11 million in 1975 to 124 million in 2016, and 213 million were overweight in 2016 [3].

The rapid increase in obesity rates was due to a combination of less active lifestyles and the inability to reduce energy consumption in line with a decrease in overall energy loss as a result of reduced physical activity. Since 1980, the prevalence of obesity has doubled in more than 70 countries, with growth rates being faster among children. The prevalence of childhood obesity has increased eight times since 1975 [4], and the combined prevalence of overweight and obesity already reached 23% worldwide, with the frequency of obesity increasing significantly after adolescence. In addition, most obese children continue to suffer in adulthood, and the risk of obesity in adulthood increases by five times compared with that in normal weight children [5].

In our country, the number of children with this pathology has also sharply increased. Thus, for children's population groups in the north-west of the European part and the Cisurals, the prevalence of overweight and obesity between 1994 and 2005

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accounted for 4–9%, and from 2008 to 2018, this indicator increased to 12.9–26.1% [6]. The prevalence of the disease in various regions of the Russian Federation depended on the gender and age of children and not on the regions of their residence. On average, the frequencies of overweight and obesity were 19.9% and 5.6%, respectively [7].

Overweight and obesity are risk factors for developing metabolic syndrome, and in recent years, they have become a worldwide major public health problem, affecting both children [8] and adults in almost all countries.

In 50–60% of cases, overweight and obesity in children also persist in the following time, which in turn increases the risk of developing concomitant diseases associated with obesity in adulthood [9]. Concomitant diseases can be multiple, and premature mortality and morbidity, associated primarily with cardiometabolic syndromes, represent the most significant economic and social hazard to public health under the "epidemic" of obesity [10].

Obesity in children and adolescents is associated with unfavorable physical and psychological consequences that can occur in childhood and are subsequently registered in adults [11, 12]. The short-term effects include metabolic disorders such as high blood pressure, dyslipidemia, insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus (DM2), steatohepatitis (nonalcoholic fatty liver disease) and metabolic syndrome [11–13], endocrine disorders (e.g., progressive pubertal development and polycystic ovarian syndrome), respiratory symptoms (e.g., dyspnea and obstructive sleep apnea syndrome), orthopedic complications (e.g., displacement in the main epiphysis of the femoral bone, Blount disease, valgus knee, and platypodia) [14], and malignant neoplasms [12, 13].

Metabolic syndrome is a cluster of cardiometabolic disorders, which together represent additional risk factors for cardiovascular disease and DM2. The syndrome is more common in overweight people and affects a relatively small proportion (3–4%) of young people with normal body weight and 26–50% of children and adolescents with obesity. It should be noted that not all obese young people develop metabolic syndrome, although up to 90% will have at least one component. However, a significant minority will remain metabolically healthy [15].

In the long term, obesity in children increases the risk of developing pathologies such as cardiovascular diseases, DM2, and some cancer types [9, 12]. Psychologically, obese children usually suffer from negative body perception and low self-esteem [11], which often turns into anxiety and depression in adulthood [12]. Consequently, the early prevention of overweight and obesity is increasingly recognized as a vital strategy to reduce the risk of complications associated with this disease.

Methods for determining obesity. Appropriate methods are required to identify children at risk for obesity. There are many tools available to assess body composition, but none of them are direct. Each technique has its limitations, and a combination of techniques can be used.

The main clinical indicators are body weight, height, body mass index (BMI), and the circumferences of different body parts, which provide sufficient information on classifying overweight or obesity when centile diagrams of height and its body weight relation are used. The thickness of skin folds is cost-effective but requires technical training and evaluates subcutaneous fat only [16].

BMI is calculated as the ratio of body weight in kilograms to the square of a person's height expressed in meters. It has been significantly confirmed that BMI has a direct correlation with the amount of adipose tissue in the body in both adults and children [17]. The manifestation rate of overweight is determined according to percentile tables or standard deviations (SDs) of BMI. They take into account height and body weight, depending on the child's gender and age. This is because the BMI value in childhood changes with child development, from a high value in the first 12 months of life to decreased during early childhood (2–5 years), with a gradual increase in puberty, which generally reflects the dynamics of changes in the amount of fat tissue.

Based on the body weight, height, BMI calculation, BMI percentile, and BMI z-score determination, normal body weight was defined as a BMI z-score between –1.00 and +1.00, whereas malnutrition as BMI lower than –2.0 SD. Also, a BMI z-score from +1.00 to +2.00 was considered as overweight and greater than 2.00 as obesity.

At present, the analysis of bioelectric impedance (bioimpedansometry) is also widely used in clinical practice. This method is based on differences in the electrical conductivity of body tissues due to different contents of liquid and electrolytes in them, allowing estimation of quantitatively different components of the body composition based on the measured electrical resistance (impedance). According to the results of bioimpedansometry in combination with the methods of mathematical modeling, included in the analyzer software, the indicators that are clinically significant for idiopathic obesity can be determined, namely, the total body water content, active cell mass amount, adipose tissue amount, and basal metabolic rate.

Other methods available for assessing obesity include dual-energy X-ray absorptiometry, air-

displacing plethysmography, magnetic resonance imaging, computed tomography, and ultrasound examination [16]. Dual-energy X-ray absorptiometry and air-displacing plethysmography could determine obesity accurately but are unable to distinguish fat deposits. Magnetic resonance imaging and computed tomography can distinguish between intra-abdominal obesity and subcutaneous obesity, and they are considered the gold standards. However, computed tomography is not suitable for determining obesity in children because of its high radiation exposure level. Ultrasound examination is a promising method to assess intra-abdominal obesity in children, but it is prone to variability, depending on the operator. The use of this method in obese patients remains a matter of debate. In addition to the high cost of some of these methods, many cannot be used in childhood because of the nature of the technique, which requires the child to remain motionless for long periods, possible secondary effects, the need for the subject's mutual work, and the lack of valid reference standards for children and adolescents [16].

In clinical settings, the commonly used methods are indirect but simple, quick, noninvasive, easily feasible, cost-effective, and without risk to patients. These methods include anthropometry and bioimpedansometry [18].

Pathophysiology of obesity. Body weight is regulated by various physiological mechanisms that maintain a balance between consumption and energy loss. These regulatory systems under normal conditions, such as a positive energy balance of only 500 kJ (120 kcal) per day (approximately one portion of sugar-sweetened soft drink), would lead to an increase in body weight of 50 kg over 10 years. Thus, factors that can increase energy consumption or reduce its loss cause obesity in the long term [19].

Obesity can result from a prolonged energy imbalance between nutrient intake and activity, with physical activity and a sedentary lifestyle affecting the latter [20]. Behavioral factors include excessive food intake and high-caloric sugar-sweetened low-nutritional drink consumption that are easily available to children. Lack of physical activity also contributes to obesity. Children spend a lot of time using devices such as mobile phones, televisions, computers, or video games, do not have physical activity, and do not participate in active games. These behavioral factors can become one of the main factors in the prevention and treatment of childhood obesity [21].

However, obesity results from a complex interaction between genetic, epigenetic, environmental, and behavioral factors.

Obesity is associated with an increase in insulin resistance, which causes an increase in glucose formation in the liver and a decrease in glucose uptake in the muscles and adipose tissue. At the same time, developing pancreatic β-cell dysfunction occurs, which prevents a compensatory increase in insulin secretion. The combination of resistance to insulin and the loss of a compensatory response to insulin lead to the development of DM2. The incidence of DM2 has changed consistent with the incidence of obesity, and some clinics currently report that 45% of all new DM2 cases are children and adolescents. There is evidence of a genetic predisposition to high-risk insulin resistance registered in populations in the Middle East and Asia (especially China and India), with the development of DM2 at a lower BMI and at a younger age, compared with that in the Western populations. More detailed genetic studies currently reveal that variants of at least 13 genes are associated with significant variations in insulin resistance [22].

Iranian studies in adults have shown that polymorphic variants of the genes *APOC3*, *APOA1*, *MC4R*, and *cyclin D2* can be significant [23,24]. In some cases, overweight and obesity can be caused by birth defects, such as genetic abnormalities. Numerous genetic mutations were associated with the development of severe monogenic obesity (involving factors such as the brain-derived neurotrophic factor, leptin, leptin receptor, melanocortin-4 receptor, and proopiomelanocortin) [25]. In addition, obesity is associated with several genetic syndromes, including Prader–Willi syndrome, Alstrom syndrome, and Biedl–Bardet syndrome.

For some of these rare forms of obesity, which account for less than 5% of all cases, 16 targeted treatment methods were found (e.g., leptin with its congenital deficiency, α-melanocyte-stimulating hormone analog 17 with proopiomelanocortin deficiency, and the Biedl–Bardet syndrome) [26]. However, true monogenic obesity with the possibility of using targeted therapy is rare. In most cases, obesity is polygenic; therefore, targeted therapy is currently not possible. In addition, the mechanisms by which genetic variants contribute to the development of obesity are largely unknown.

In most cases, BMI is hereditary. As a result of a meta-analysis of a genetic study by the Anthropometric Traits Consortium (GIANT), 97 loci associated with BMI were detected in adults of European ancestry, which is 2.7% of BMI variability [27]. In total, more than 250 loci associated with BMI were found in adults of African, East Asian, and European ancestry [28], and many of these loci were also identified in children [29]. The GIANT consortium additionally found 941 nearly independent

single nucleotide polymorphisms associated with BMI among adults of European ancestry, accounting for 6% of the BMI dispersion [30].

These findings suggest that although many loci and independent single-nucleotide polymorphisms are important in the heritability of BMI, most genetic sources for variability in BMI remain unknown. Ethnic and population differences certainly underlie a genetic predisposition to the development of obesity [31]. Twin studies reveal that BMI is inherited and highly susceptible to genetic factors. The Genomic Association (GWAS) has successfully identified associated loci, and many of which are involved in controlling body weight and appetite through the central nervous system [27]. However, loci identified by GWAS account for less than 10% of heritability. In recent years, rare variations in the number of copies affect the etiology of numerous conditions, including autistic disorders, type 1 diabetes mellitus, congenital heart defects, and growth disorders in children [32]. Variations in the number of copies have also been described in the pathogenesis of obesity, which underlines the potential role of another type of genetic contribution [33].

Epidemiological studies of the mechanisms involved in genetic inheritance have shown that FTO gene polymorphism may be associated with obesity, and data suggest that children and adolescents with FTO rs9939609 gene polymorphism, especially those with AA and AT risk alleles, can be more prone to obesity [34]. Biological factors, such as a family history of obesity, including paternal and maternal obesity, overweight at birth, and the presence of adipose mass and the rs9939609 polymorphism associated with obesity, have been associated with overweight/obesity in children and adolescents [35].

Although genetic disorders acting in isolation can hardly explain the rapid increase in the prevalence of obesity in recent decades, it is possible that a genetic predisposition, combined with environmental and behavioral factors, may contribute to the development of obesity [36]. Other biological factors, such as hormonal, endocrine, and microbiological disorders, can also have an independent and/or synergistic effect on the development of obesity [37].

It must be noted that the above potential causes of obesity cannot be considered exhaustive, and other conditions are also associated with its development. These include prenatal weight gain and the presence of gestational diabetes in the mother's history, gestational weight, medications associated with weight gain, environmental toxins, microbiomes, transcriptomes, human proteomes [38,39], and psychosocial determinants, for example, the impact of advertising "healthy" fast food, which increases children's appreciation for fast food [40].

The socioeconomic situation has a direct impact on food quality and living conditions, including access to physical activity and education. Cameron et al. reported that children with a lower socioeconomic level status had a stronger weight gain trajectory that started at birth and led to a higher prevalence of obesity in children and adults.

Maternal BMI before pregnancy, diabetes mellitus, diet before pregnancy, smoking during pregnancy, low birth weight, onset and duration of breastfeeding, early addition of solid food, diet quality of the mother and baby, and some aspects of the home food environment are predictors of obesity related to socioeconomic status. Also, lack of physical activity is an additional risk factor for obesity [41]. Access to physical activity resources is directly related to higher physical activity in free time in children and adolescents and reduces the risk of obesity.

One of the potential indicators that can contribute to the development of obesity is a gastrointestinal microbiome, which has a significant effect on the metabolism of the whole organism and the development of obesity. Increased *Firmicutes* and reduced *Bacteroidetes* correlate with overweight and obesity in children [42]. *Bacteroidetes* proved to be a better predictor of BMI than *Firmicutes*, possibly because of the higher variability of *Firmicutes*. This phenomenon may explain the results of a study of microbiome profiling in eight obese children, which showed that the above tendency was noted in *Bacteroidetes* type bacteria, whereas insignificant changes were recorded in *Firmicutes* compared with the control group [43].

Metagenomic tests to establish the relationship between obesity and intestinal microbiota enables to identify specific bacterial strains as potential biomarkers of obesity and the development or progression of obesity.

Dominant bacterial types that are sequentially identified in the intestines of healthy people include *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*, and there are lower amounts of *Verrucomicrobia* and *Proteobacteria* [44]. It has been recently described that microbiota markers in adolescents and adult obese patients exhibit different age-related features [45]. *Faecalibacterium prausnitzii* and *Actinomyces* are specially assigned to the microbiota of obese adolescents, and *Bacteroides caccae*, *Barnesiellaceae*, *Parabacteroides*, *Rikenellaceae*, and *Oscillospira* belong to the microbiota of adolescents with normal body weight. *F. prausnitzii* is involved in the fermentation of undigested carbohydrates, and

the abundance of these microorganisms in the intestines of obese adolescents can increase energy recovery, leading to higher consumption of dietary energy, which in turn can contribute to the lower success of weight loss diets offered to people with a higher content of *F. prausnitzii* [46].

The action of antibiotics has an overwhelming effect on the intestinal microbiota. Epidemiological studies have shown that the consumption of antibiotics is associated with children with a risk of obesity. In addition, several studies report a correlation between BMI in childhood and the risk of developing obesity later in life with antibiotics intake [47].

It was demonstrated that the content of short-chain fatty acids, the end products of fermentation of dietary fiber by anaerobic intestinal microbiota, is higher in obese children [48], which indicates intestinal dysbacteriosis and its exacerbation; therefore, intestinal fermentation should be considered as one of the factors affecting the etiology of obesity in children. In a study by Nicolucci et al., the use of prebiotics has been shown to alter intestinal microbiota and reduce lipid deposits in obese or overweight children [49].

Personalized nutrition, the use of prebiotics, probiotics, postbiotics, and synbiotics [50], transplantation of fecal microbiota [51], dietary education, and physical activity [52] are the main approaches aimed at using the intestinal microbiota as a therapeutic target for obesity in children. A prospective study of 70 obese pediatric patients revealed that intestinal dysbiosis and dietary habits correlated with excessive body weight gain [53].

The etiology of obesity has been linked to various factors, such as dietary, environmental, educational, and genetic. However, these factors do not fully explain the global gradual increase in the incidence of obesity, and it has recently been shown that the characteristics of microbiota play a causative role in obesity [54], demonstrating the microbiota potential in the therapeutic target for obesity.

Conclusion. Overweight and obesity in children and adolescents are significant health problems of the XXI century. Obesity is a complex disease, with many contributing environmental, biopsychosocial, genetic, and epigenetic factors. It causes significant medical, psychosocial, and neurocognitive impairment in childhood. Preservation of obesity in adulthood makes understanding the causes of childhood obesity extremely important to prevent its impact on long-term health and quality of life [55].

Obesity in children is associated with a high risk of cardiometabolic syndromes, and it also indicates subclinical atherosclerosis, DM2, and insulin resistance, which starts in childhood. The cumulative severity and obesity severity are recognized as primary mediators of worsening cardiovascular and metabolic outcomes. A decrease in obesity severity has a positive effect on cardiovascular risk markers and delays or prevents cardiometabolic disease onset in the future [56].

There is evidence that changes in the intestinal microbiota may contribute to the pathogenesis of obesity and the development of metabolic disorders associated with obesity, including DM2, non-alcoholic fatty liver disease, metabolic syndrome, and cardiovascular diseases. Changing the composition of the intestinal microbiota can potentially provide an additional mechanism for achieving stable weight loss [57].

Treatment of obesity in the early stages before the onset of concomitant diseases can prevent its development into serious clinical and psychosocial problems [58].

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