OBESITY IN CHILDHOOD AND ADOLESCENCE, GENETIC FACTORS

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Abstract
Obesity and overweight are a pandemic phenomenon in the modern world. Childhood and adolescent obesity often ends up in obesity in adults. The costs of obesity and its consequences are staggering for any society, crippling for countries in development. The etiology is complex, but most often idiopathic. Hormonal, syndromic and medication-induced obesity are well investigated. Genetic causes are increasingly described. Novel technologies such as whole exome sequencing identify ever more candidate genes influencing or causing obesity. All insights into the complex problem of obesity in a team approach to treatment: diet, psychology, medications and surgery. We briefly review epidemiology, etiology, consequences and treatment approaches in childhood and adolescent obesity, with special emphasis on emerging knowledge of its genetics.

Key words: obesity, children, adolescents, obesity consequences, genetic causes.

Introduction
Obesity is a pandemic affecting at least 250 million people (7% of the estimated current world population). In addition there are at least 2–3 times more people that are overweight. Obesity is pandemic among children too. Some 21–24% of American children and adolescents are overweight and another 16–18% obese. It is of note that the prevalence of obesity worldwide is increasing. For example, the prevalence of overweight children and adolescents in the United States has increased by 50–60% in a single generation, while the prevalence of obesity has doubled. The prevalence of obesity in American Indians, Hawaiians, Hispanics and blacks is 10–40% higher than in whites [1]. The majority of adults in some societies are overweight. In the United States, 61 percent of all adults are overweight. In Russia, the figure is 54 percent; in the United Kingdom 51 percent; and in Germany 50 percent. For Europe as a whole, more than half of those between 35 and 65 years of age are overweight [2]. Adolescent obesity is predictive of adult obesity. Some 80% of teenagers who are obese continue to be obese as adults. The prevalence of obesity is high in Macedonia too [3].

Obesity is costly for any society: some estimates suggest that the management of obesity in the USA costs approximately $100 billion yearly.

Criteria
There are various methods based on weight, weight-height and skinfold thickness, each having advantages and disadvantages. Widely accepted criteria are those proposed by the World Health Organization (WHO). WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI. WHO criteria for obesity in childhood and adolescence are based on BMI.
BMI of 25–29.9 kg/m², grade 2 overweight (obesity) is a BMI of 30–39.9 kg/m² and grade 3 overweight (severe or morbid obesity) is a BMI greater than or equal to 40 kg/m². In addition, there are surgical definitions which describe a BMI greater than 40 kg/m² as severe obesity, a BMI of 40–50 kg/m² is termed morbid obesity, and a BMI greater than 50 kg/m² is termed super obese.

Pathophysiology

The simplest explanation is that obesity is the result of energy imbalance between excessive energy intake and/or reduced energy expenditure (sedentary lifestyle). Excessive television viewing and/or excessive computer use, and insufficient physical activity particularly influence the chances of obesity in children and adolescents. In infancy, excess fat deposition occurs when excess energy is provided, especially when the protein-to-energy ratio is altered. Excess weight in children depends on both genetic and environmental factors.

Etiological factors are multiple. It is of note that > 90% of cases are idiopathic, < 10% are associated with hormonal or genetic causes. Among hormonal disorders there are: growth hormone deficiency and growth hormone resistance, hypothyroidism, leptin deficiency or resistance to leptin action [4–6], glucocorticoid excess (Cushing syndrome), precocious puberty, polycystic ovary syndrome (PCOS) and prolactin-secreting tumours. Many medications can cause overweight/obesity: glucocorticoids, insulin, sulfonylureas, risperidone, thiazolidinediones, clozapine, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs: e.g phenelzine) and oral contraceptives. Finally, syndromes such as Bardet-Biedl syndrome, Prader-Willi syndrome, pseudohypoparathyroidism, Cohen syndrome, Down syndrome and Turner syndrome are among those in which obesity is or can be a part of the clinical manifestations. Recently, other genetic causes have been described: POMC splicing mutation [7], prohormone convertase-1 Deficiency [8], melanocortin-4 receptor mutation [9], melanocortin-3 receptor mutation [10], SIM-1 mutation (SIM1 – "single-minded"). It is of note that the concordance rates for obesity and type 2 diabetes mellitus are higher in monozygotic twins than in dizygotic twins, further indicating the importance of genetic factors in the origins of obesity.

Leptin (from the Greek word leptos, meaning thin). Leptin is a 16-kD protein produced in white adipose tissue and, to a lesser extent, in the placenta, skeletal muscle, and stomach fundus in rats. Leptin has functions in carbohydrate, bone, reproductive metabolism and in body weight regulation. Leptin signals satiety to the hypothalamus. Most humans who are obese are not leptin deficient but rather leptin resistant, and have elevated circulating levels of leptin. Therefore, the dysfunction of the gut-brain-hypothalamic axis through the ghrelin/leptin hormonal pathway is thought to have a role in abnormal appetite control and excess energy intake.

About 10 patients of Pakistani and Turkish consanguineous descent have been described with hyperphagia from birth, and early obesity (6 months). The thyroid hormone levels were reduced; there was a lack of sympathetic tone, a lack of pubertal progression. In addition the immunity was defective. Patients were short and lacked the pubertal growth spurt. Impressively, treatment with recombinant leptin restores leptin signalling, and results in reduction of hyperphagia, resolution of obesity, induction of puberty, and restoration of immune regulation [6].

Leptin Receptor Deficiency patients are similar to those with leptin deficiency. However, they might have growth retardation, low IGFl and IGFBP-3 levels and low thyroid levels.

Proopiomelanocortin (POMC) and alpha-melanocyte-stimulating hormone (alpha-MSH) act centrally on the melanocortin receptor 4 (MC 4) to reduce dietary intake. Patients with POMC mutations tend to have red hair, and central adrenal insufficiency [7]. Strikingly, as many as 5% of children who are obese have MC4 or POMC mutations.

In prohormone convertase deficiency, patients have clinically significant obesity, hypogonadotropic hypogonadism, and central adrenal insufficiency [8].

PPAR-gamma. Patients with mutations of the receptor (at band 3p25) described so far have severe obesity.

Melanocortin-4 Receptor Mutation. Mutations in the MC4R appear to account for up to 5% of morbid obesity in childhood. This mutation is transmitted as a co-dominant inheritance.
Melanocortin-3 Receptor Mutation. As in MC4R diagnosis can only be made by gene sequencing.

FTO ("fat mass and obesity associated" gene). FTO expression is high in regions of the hypothalamus involved in energy balance and its expression levels are regulated by variations in food intake. In humans, a genome-wide association study involving nearly 39,000 people found that people with 2 copies of an FTO variant weighed an average of 3 kg more than did people with no copies of that variant. Individuals with 2 copies of the variant were 67% more likely to be obese than people without the variant [11].

Nevertheless, individuals with these FTO variants can, with increased physical activity, offset the genetic predisposition to obesity associated with the FTO polymorphism [12].

Genome-wide linkage analyses and microarray technology have revealed a rapidly growing list of potential obesity susceptibility genes: chromosome arms 2p, 10p, 5p, 11q, and 20q.

Other causes. It has also been suggested that inflammatory and infective etiology may exist for obesity. Namely, adenovirus 36 infection is associated with obesity in chickens and mice. Humans who are not obese have a 5% prevalence of adenovirus 36 infection, while humans who are obese have a prevalence of 20–30%.

Co-morbidities and complications

Obesity has a considerable impact on quality of life, and some reduced life expectancy. Co-morbidities and complications are severe:

1. Cardiovascular: essential hypertension, coronary artery disease, left ventricular hypertrophy, cor pulmonale, cardiomyopathy, accelerated atherosclerosis, pulmonary hypertension.
2. CNS: stroke, idiopathic intracranial hypertension, meralgia paresthetica.
3. GI: cholecystitis, cholelithiasis, steatohepatitis, fatty liver infiltration, reflux oesophagitis.
4. Respiratory: obstructive sleep apnea, (Pickwickian syndrome), increased predisposition to respiratory infections, increased incidence of bronchial asthma.
6. Psychological: social isolation, peer problems, depression.
8. Metabolic: insulin resistance, hyperinsulinaemia, type 2 diabetes mellitus, dyslipidaemia. The rate of increase in BMI during adolescence may be a significant risk factor for diabetes [13, 14].
11. Surgical: increased surgical risk and postoperative complications.
12. Miscellaneous: reduced mobility, difficulty maintaining personal hygiene, Stress incontinence, Intertrigo (bacterial and/or fungal), acanthosis nigricans, hirsutism, increased risk of cellulitis and carbuncles, venous varicosities, lower extremity venous and/or lymphatic edema.

Treatment

The team approach to therapy (nurse educators, nutritionists, exercise physiologists, and counsellors) is the basis for treatment. Dramatic reductions in BMI are difficult to achieve and sustain so counselling and therapy should start with realistic goals that emphasize gradual reductions in body fat and BMI and maintenance of weight loss [15].

Family-based behavioural weight control is effective for severely obese children [16]. Active participation and support of family members is necessary if treatment is to be successful. Children should be encouraged to participate in vigorous physical activity and to limit time spent watching television and playing computer games.

The European Youth Heart Study confirms that improving fitness habits in children correlates with a lower incidence of obesity in adolescence [17]. Controlled trials have demonstrated lifestyle exercise programmes, in association with dietary restrictions. The team approach to therapy (nurse educators, nutritionists, exercise physiologists, and counsellors) is the basis for treatment. A very con-
trolled-energy diet is not to be recommended for the majority of children and adolescents.

Medication. Some medicaments have been also used as adjunct interventions. Sibutramine (Meridia), a selective serotonin norepinephrine reuptake inhibitor, and orlistat (Alli, Xenical), a pancreatic lipase inhibitor, are approved for use. Sibutramine may be classified as an anorectic drug, whereas orlistat's mechanism of action involves induction of lipid malabsorption. Benzphetamine (Didrex), diethylpropion, phendimetrazine (Bontril), and phentermine (Ionamin) have also been used. The serotoninergic drugs fenfluramine and dexfenfluramine (Ionamin) have also been used. The serotoninergic drugs fenfluramine and dexfenfluramine were recently withdrawn because of their cardiodynamic effects [20].

Pediatric experience with the use of weight-loss drugs has conflicting results (reduction and failure to reduce fat). Guidelines for the prevention and treatment of childhood obesity have been released. Orlistat yielded conflicting results [18, 19]. A randomized placebo-controlled trial of sibutramine in 498 adolescents demonstrated a significant reduction in body mass index (BMI), without any observed cardiodynamic effects [20].

Surgical Care. Various bariatric surgical procedures have been used in adults and some adolescents (in most centres, patients > 15 y) with a BMI of more than 40 or weight exceeding 100% of ideal body weight (IBW).

In the vertical-banded gastroplasty (VBG), a pouch of 15-mL to 30-mL capacity is constructed, greatly reducing the amount of food that can be eaten at any time. In the gastric bypass, a larger pouch that empties into the jejunum is created. Laparoscopic placement of an adjustable gastric band (LAGB) has supplanted the VBG because of its relative safety and because of its reversibility. LAGB places a collar with an internal, saline-filled balloon around the upper stomach, 1–2 cm below the oesophagogastric junction.

REFERENCES


Резиме

ОБЕЗИТЕТ ВО ДЕТСТВОТО И АДОЛЕСЦЕНЦИЈАТА: ГЕНЕТСКИ ФАКТОРИ

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Дебелината и прекумерната тежина се пандемски проблем во модерниот свет. Дебелината во детството и адолесценцијата често завршува со дебелина и во зрелоста. Здравствените трошоци на дебелината и нејзините последици се значителни за секое општество, енормни за земјите во развој. Етиологијата е комплексна, но најчесто идиопатска. Хормонална, синдромската и дебелината предизвикана од медикаменти се добро истражени. Генетските причини се многубројни и се почето се откриваат нови генетски фактори за настанок на дебелината. Новите технологии како што е секвенцирането на целото егзом (whole exome sequencing) пронајдат повеќе гени кандидати кои влијаат или предизвикуваат дебелина. Во комплексниот проблем на дебелина важен е тимски пристап во лекувањето и комбиниран и селекционар избор на диета, психологски интервенции, лекови и хирургски третман. Овој труд е краток осврт кон епидемиологијата, етиологијата, последиците и третманот на детската и адолесцентната дебелина, со посебен акцент на најновите знаење за нејзината генетика.

Ключни зборови: дебелина, деца, адолесценти, последици од дебелината, генетички причини.