Associations of GHRL gene variants with the development of obesity and metabolic disorders in children


Abstract. Background. Single nucleotide variants (SNVs) of the ghrelin (GHRL) gene are accompanied by the production of a defective preproghrelin protein, which can lead to the development of obesity and metabolic disorders. The purpose was to study the associations of SNVs of the GHRL gene in children with the development of various obesity phenotypes. Materials and methods. Two hundred and fifty-two obese children aged 6–18 years were examined. The main group (n = 152) was represented by patients with metabolically unhealthy obesity (MUO). The control group (n = 100) included children with metabolically healthy obesity (MHO). Whole genome sequencing (CeGat, Germany) was performed in 31 children of the main group and 21 controls. Serum levels of interleukin-1β (IL-1β) were measured using a chemiluminescent immunoassay, interleukin-6 — by enzyme-linked immunosorbent assay (Synevo, Ukraine). Results. The association with the development of MUO was higher for the T allele of SNV rs696217 in healthy individuals (t = 2.31; p < 0.05) and obese patients (t = 2.06; p < 0.05). The GT genotype SNV rs696217 was associated with insulin resistance (r = 0.40; p < 0.05) in the MUO group and inversely correlated with levels of cholesterol (r = –0.45) and low-density lipoprotein cholesterol (r = –0.39) in children with MHO. The TA SNV rs4684677 genotype correlated with IL-6 levels (r = 0.74) in the MHO group and with IL-1β (r = 0.35) in children with MUO, p < 0.05. Prevention of the transformation of MHO into MUO is determined by the T allele SNV rs34911341 (t = 2.29, p < 0.05). Conclusions. The missense variants rs696217 and rs4684677 of the GHRL gene are SNVs highly associated with obesity and the development of metabolic disorders. Keywords: ghrelin; analysis of single nucleotide gene variants; children; metabolically unhealthy obesity; metabolically healthy obesity

Introduction

Over the past decades, due to the pandemic nature of the spread of obesity, the problem of its treatment and prevention of metabolic disorders in children has been in the focus of medical community [22]. Evidence has now been obtained that a sedentary lifestyle, excessive consumption of high-calorie foods, sleep disorders and genetic predisposition cause a high risk of developing polygenic obesity [2]. Mutations of genes involved in the regulation of appetite, of the activity of hedonic pathways, the formation of food preferences, carbohydrate and fat metabolism, as well as the development of adipocytes, the distribution of adipose tissue in the body may predetermine excessive accumulation of fat [1, 4, 16, 32]. According to the results of the Human Obesity Gene Map project, about 500 genes are associated with the development of human obesity, among which the ghrelin-obestatin preproprotein gene (growth hormone secretagogue receptor ligand, GHRL) is noted [8, 10, 34–39, 46]. The GHRL gene is located on the short arm of chromosome 3 (3q25-26). Structurally, the human GHRL gene consists of five exons, four introns and encodes the 117 amino acid sequence of preproghrelin [24, 39]. As a result of post-translational modifications, preproghrelin is processed to form two biologically active molecules: ghrelin, consisting of 28 amino acid residues (sequence from 24 to 51 amino acid residues of the preproghrelin molecule), and obestatin, formed by 23 amino acid residues (sequence from 76 to 98 amino acid residues of the preproghrelin molecule) [45, 50]. The orexigenic hormone ghrelin was identified in 1999 as a peptide secreted by A-like cells in the gastric mucosa. The acylated form of ghrelin has the ability to bind with...
the N-terminal region of its molecule to receptors 1α that stimulate the secretion of growth hormone (growth hormone secretagogue receptor 1α — GHSR1α), which are located on the membranes of neurons of the hypothalamus, endotheliocytes, intestinal epithelial cells, cardiomyocytes, adipocytes, β- and α-cells of the pancreas, cells of the adrenal glomeruli, osteoblasts [17, 24, 45]. A rhodopsin-like high-affinity G-protein-coupled receptor, class A GHSR1α, which has seven transmembrane α-helical domains, is activated by the acylated form of ghrelin and is blocked by liver-expressed antimicrobial peptide 2. Ghrelin-mediated induction of GHSR1α receptors, which are located on NPY/AgRP neurons, causes an increase in appetite and changes in eating behavior, while excitation of GHSR1α, which are located on other cells, preferentially activates mechanisms that promote hyperglycemia. Ghrelin inhibits insulin secretion by β-cells and stimulates the production of glucagon secretion by pancreatic α-cells, regardless of food intake, stimulates lipogenesis, inhibits thermogenesis, has a cardioprotective and antiinflammatory effect on muscle tissue [28, 29, 35, 36, 53], while obestatin, interacting with receptors such as G-protein coupled receptor 3, glucagon-like peptide-1 receptor and GHSR, causes effects opposite to ghrelin. Ghrelin stimulates appetite and growth hormone secretion, and obestatin blocks these effects. Obestatin suppresses food intake and promotes weight loss [50, 51].

Non-synonymous single nucleotide variant (SNV) of the GHR1 gene is accompanied by the production of a defective preproghrelin protein, which can lead to the development of obesity and metabolic disorders [10, 30].

However, the associations of single nucleotide variants of the GHR1 gene with obesity-related metabolic disorders remain practically unexplored.

The purpose was to study the associations of SNV of the GHR1 gene in children with the development of various obesity phenotypes.

Materials and methods

Ethical approval

Participants provided written informed consent, and research protocols and procedures were approved according to the ethical standards of the Helsinki Declaration 2013 and by the Human Research Ethics Committee of Dnipro State Medical University (ethical approval DSU/EC/19/1107). Time of data collection: January 2020 — February 2023.

Informed consent: informed consent was obtained from all individual participants included in the study.

Study design: observational, analytical, longitudinal, cohort study [44].

Inclusion criteria: polygenic obesity (BMI ≥ 97th percentile), age of 6–18 years.

Exclusion criteria: monogenic and secondary forms of obesity; hereditary syndromes accompanied by obesity; diseases whose treatment requires the use of medications that affect carbohydrate and lipid metabolism; pregnancy.

Setting. At the Children’s Endocrinology Department of the Communal Non-profit Enterprise “Dnipro City Clinical Hospital 9” of the Dnipro City Council, 252 children aged 6–18 years with a diagnosis of obesity were examined. To verify the diagnosis, the classification of obesity recommended in clinical practice was used: Order of the Ministry of Health of Ukraine No. 254 dated 27.04.2006 “Protocol for the provision of medical care to obese children” and Order of the Ministry of Health of Ukraine No. 1732 dated 24.09.2022 “About the approval of Standards of medical care “Obesity in children”.

The main group (n = 152) was represented by children with metabolically unhealthy obesity (MUO), the control group (n = 100) was formed from patients with metabolically healthy obesity (MHO).

Criteria for inclusion in the main group: the presence of abdominal obesity [3] and two of the following criteria: hyperglycemia and/or hyperinsulinemia; dyslipidemia; systolic blood pressure and diastolic blood pressure above the 90th percentile for a given age, gender and height [15].

Immunochromic examination

The studies were carried out in a certified Syneo laboratory (Dnipro, Ukraine). The material for the study was venous blood.

To study carbohydrate metabolism disorders, the level of basal glycemia and insulinemia was determined by immunochromic testing with electrochemiluminescence immunoassay. Obese children were included in the main group with a glycermic level equal to or greater than 5.6 mmol/L and/or they had an increase in insulinemia above 90th percentile according to the percentile curves recommended by the IDEFGICS consortium for the European population depending on the age and gender of a child [13, 33].

To study lipid metabolism disorders, the level of high-density lipoproteins (HDL-C), low-density lipoprotein cholesterol and triglycerides was determined by the enzymatic colorimetric method using Roche Diagnostics kits (Switzerland) on the Cobas 6000 analyzer. Obese children were included in the main group with HDL-C ≤ 1.03 mmol/L or less than 10th percentile of the age norm or an increase ≥ 1.7 mmol/L or more than the 90th percentile of the age norm [14].

Molecular and immunochromic examination

To study the role of pro-inflammatory markers in the development of meta-inflammation in childhood obesity, serum levels of IL-1β, IL-6 were determined in the certified Syneo laboratory (Dnipro, Ukraine). Interleukin-1β was investigated by immunochromic method with chemiluminescence immunoassay. Analyzer and test system was Immulite (Siemens AG, Germany). The reference IL-1β value was 0–5 pg/ml. Interleukin-6 was determined by enzyme-linked immunosorbent assay using a Cobas 6000/Cobas 8000 kit provided by Roche Diagnostics (Switzerland). The reference IL-6 value was 1.5–7.0 pg/ml.

Molecular genetic testing

To study the contribution of GRLN SNV variants to the formation of MUO, a molecular genetic examination was carried out using the method of next generation sequencing according to the recommendations of The American College of Medical Genetics and Genomics [12] in 52 patients (31 children from the main group and 21 controls) with venous blood sampling in a certified CeGat laboratory (Tubingen, Germany) using the Illumina CSDPro® Certified Service Provider Program.

Average amount of DNA (μg) in samples was 0.875. Library Preparation: quantity used 50 ng. Library Preparation
**Results**

Whole genome sequencing of obese children identified four SNV of the **GHRL** gene: rs696217, rs4684677, rs34911341, and rs139684563. The distribution of genotype frequencies was in Hardy-Weinberg equilibrium in both groups of obese children.

Molecular genetic characteristics of the identified SNV of the **GHRL** gene are presented in Table 1.

The most highly pathogenic among the identified SNV of the **GHRL** gene are three nonsynonymous variants rs696217, rs4684677, rs34911341 (CADD = 22.6, 24.3, 25.5, respectively).

**Table 1. Characteristics of SNV types of the GHRL gene**

<table>
<thead>
<tr>
<th>SNV, ID</th>
<th>Position</th>
<th>GnomAD_maxPOP</th>
<th>Ref</th>
<th>Alt</th>
<th>Consequence</th>
<th>Base change</th>
<th>CADD</th>
<th>RawScore</th>
<th>Clinical significance (ClinVar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs696217*</td>
<td>10331457</td>
<td>NFE</td>
<td>G</td>
<td>T</td>
<td>Missense</td>
<td>c.175C&gt;A</td>
<td>22.6</td>
<td>2.5</td>
<td>Likely benign</td>
</tr>
<tr>
<td>rs4684677*</td>
<td>10328453</td>
<td>AFR</td>
<td>T</td>
<td>A</td>
<td>Missense</td>
<td>c.116A&gt;T</td>
<td>24.3</td>
<td>3.27</td>
<td>Benign</td>
</tr>
<tr>
<td>rs34911341</td>
<td>10331519</td>
<td>NFE</td>
<td>C</td>
<td>T</td>
<td>Missense</td>
<td>c.113G&gt;A</td>
<td>25.5</td>
<td>3.63</td>
<td>Risk factor</td>
</tr>
<tr>
<td>rs139684563</td>
<td>10334546</td>
<td>NFE</td>
<td>C</td>
<td>T</td>
<td>Missense</td>
<td>c.52G&gt;A</td>
<td>4.57</td>
<td>0.12</td>
<td>Not reported in ClinVar</td>
</tr>
</tbody>
</table>

**Notes:** GnomAD_maxPOP — the frequency distribution of GHRL mutations; Ref — reference allele; Alt — alternative allele; Consequence — functional consequence of the variation in relation to the transcript. The nucleotide change and position relative to the coding sequence of the affected transcript in HGVS nomenclature: c. — CDS Position Reference Base &gt; Alternative Base. Example: c.223A>T (c.1 — interpretation for DNA coding sequence) [40]. This column is empty if the variant is intergenic; CADD — combined annotation dependent depletion; * — SNV GHRL associated with MUO; AFR — African; NFE — non-Finnish Europeans.

**Associations of SNV GHRL gene with obesity phenotypes in children**

The frequency of occurrence of SNV of the **GHRL** gene in children with different obesity phenotypes is presented in Table 2.

In children with the MUO phenotype, the frequency of the mutant T allele for SNV rs696217 of the **GHRL** gene was significantly higher than the frequency of this polymorphism among healthy Europeans of non-Finnish origin ($t = 2.31; p < 0.05$) and children with the MHO ($t = 2.06; p < 0.05$).

According to the analysis data, the frequency of the T allele SNV rs34911341 of the **GHRL** gene in children with the MUO phenotype was significantly lower than in patients with the MHO ($t = 2.29; p < 0.05$).

**Associations of SNV GHRL gene with inflammatory activity**

Correlation analysis revealed that production of pro-inflammatory cytokines in obese children depended on the SNV rs4684677 genotype of the **GHRL** gene. Thus, the AT genotype SNV rs4684677 in children with MHO was highly associated with the level of IL-6 ($r = 0.74$), and in patients with MUO — with IL-1β concentration ($r = 0.35$) in the blood serum. Carriers of the A allele compared with non-carriers had a higher level of pro-inflammatory interleukins.

**Associations of SNV GHRL gene with disorders of carbohydrate metabolism**

It was found that of all SNV of the **GHRL** gene identified in patients with obesity, only rs696217 genetic variant was associated with carbohydrate metabolism disorders. This association was noted exclusively in children with MUO. SNV rs696217 of the **GHRL** gene appeared to be moderately associated with the HOMA index ($r = 0.40$). Children with the MUO and the GT genotype SNV rs696217 of the **GHRL** gene had a higher HOMA index than those with the MHO phenotype and the wild GG genotype of SNV rs696217 **GHRL** gene.

**Associations of SNV GHRL gene with lipid metabolism disorders**

It was found that SNV rs696217 of the **GHRL** gene in children with the MHO phenotype is inversely related to
the serum level of cholesterol and low-density lipoprotein cholesterol: $r = -0.45$; $r = -0.39$. The remaining identified SNV of the GHRL gene were not associated with the blood lipids of obese children.

**Discussion**

According to the results of whole genome sequencing, SNVs rs696217, rs4684677, rs34911341, and rs139684563 of the GHRL gene are found in obese children. Three non-synonymous variants rs696217, rs4684677, rs34911341 have a high level of pathogenicity (CADD = 22.6, 24.3, 25.5, respectively). It should be noted that the presence of SNV rs139684563 of the GHRL gene in obesity was revealed by us for the first time. The missense mutation rs139684563 (C>A, T), which is accompanied by the replacement of a glycine residue with an arginine residue at position 18 (Gly18Arg) of the preproghrelin molecule, is very rare in the European population (AF = 0.08 %) [21]. In children with the MUO phenotype, the frequency of the T allele SNV rs696217 of the GHRL gene was significantly more common than in healthy Europeans of non-Finnish origin and children with the MHO.

We found that SNVs rs696217, rs4684677 of the GHRL gene are associated with pro-inflammatory status and metabolic markers in obese children. Also, E. Becer and M.C. Ergoren believe that SNVs of the GHRL gene are associated with the development of obesity and metabolic syndrome in adults [5]. However, according to the results of C. Bing et al. [6], the SNV rs696217 of the GHRL gene has no effect on the development of metabolic disorders in obese adults.

It was shown that the missense variant of SNV rs696217 (G>T), located in the second exon of the GHRL gene, leads to the replacement of a leucine with a methionine residue at position 72 (Leu72Met) of the preproghrelin molecule [30]. The SNV rs696217 of the GHRL gene is believed to be highly associated with the development of obesity. According to E. Becer and M.C. Ergoren [5], the T allele of SNV rs696217 of the GHRL gene is significantly associated with waist and hip circumferences. In the Turkish Cypriot population, the frequency of occurrence of the minor T allele SNV rs696217 in obese individuals is significantly higher than in people with physiological body weight. Individuals with the GT or TT genotype are at higher risk of developing obesity compared to those with the GG genotype SNV rs696217 [52]. A low-calorie diet as a treatment for obesity in female individuals with SNV rs696217 of the GHRL gene does not result in weight loss [42]. We found that the GT SNV rs696217 genotype of the GHRL gene is associated with markers of metabolic disorders in obese children. In persons with metabolic syndrome, the frequency of the T allele of the currently most studied SNV rs696217 of the GHRL gene is 8.6 % [6]. According to our data, this level of occurrence of the T allele SNV rs696217 of the GHRL gene is typical for children with the MHO phenotype, and in children with the MUO, it reaches 19 %. In the MUO, the GT SNV rs696217 genotype contributes to the development of insulin resistance, and in the MHO, this genotype prevents the development of dyslipidemia. The results of studies on the relationship between SNV rs696217 of the GHRL gene and the risk of developing carbohydrate metabolism disorders are controversial. According to the research by E.A. Rivera-León et al. [41], the G allele of SNV rs696217 of the GHRL gene was more common in type 2 diabetes mellitus (T2DM). At the same time, F.E. Joatar et al. [23], J. Liu et al. [27] emphasize the absence of association between SNV rs696217 of the GHRL gene and the risk of developing T2DM. Buraczynska M. et al. [7] also did not find a significant association between SNV rs696217 of the GHRL gene and the risk of developing T2DM, but showed that the presence of the T allele of SNV rs696217 is associated with a higher risk of hypertension (OR = 2.50, 95% CI 1.68–3.73, p < 0.001). Regarding the association of SNV rs696217 of the GHRL gene and the blood lipids, M. Su et al. [47] demonstrated that after a high-carbohydrate diet, carriers of the SNV rs696217 T allele of the GHRL gene had a significantly lower serum triglyceride/HDL ratio than those with the wild genotype. Also, the T allele (Met72) compared to the G allele (Leu72) is associated with a lower risk of developing metabolic-associated liver disease [48].

According to our data, SNV rs4684677 of the GHRL gene was not associated with either the development of obe-

<table>
<thead>
<tr>
<th>SNV</th>
<th>GnomAD browser, %</th>
<th>The frequency of major and minor options, %</th>
<th>The value of Student’s t-test in Welch’s modification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Popmax AF (HET/ HOM&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>AF NFE, (HET/HOM&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>MHO (HOM&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>rs696217</td>
<td>9</td>
<td>81</td>
<td>0.25</td>
</tr>
<tr>
<td>rs4684677</td>
<td>10</td>
<td>94</td>
<td>0.31</td>
</tr>
<tr>
<td>rs34911341</td>
<td>0.8</td>
<td>100</td>
<td>1.67</td>
</tr>
<tr>
<td>rs139684563</td>
<td>0.4</td>
<td>97</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Notes: HOM<sup>a</sup> — homozygous variant (biallelic single nucleotide substitution); HET — heterozygous variant (single allelic single nucleotide substitution); Popmax AF — maximum population allele frequency in the genome (gnomAD browser); AF NFE — allele frequency for non-Finnish Europeans in the genome (gnomAD browser); * — critical value of Student’s t-test modified by Welch $> 1.97$ at which the differences in the compared groups are significant, $p < 0.05$; Student’s test of significance modified by Welch: $t<sub>1</sub>$ — in the comparison groups of MHO and healthy non-Finnish Europeans; $t<sub>2</sub>$ — in the comparison groups of MOU and healthy non-Finnish Europeans; $t<sub>3</sub>$ — in the MHO and MHO comparison groups.
sity or the differentiation of the obesity phenotype in children. At the same time, M. Gueorguiev et al. [18] showed the association of SNV rs4684677 of the GHRL gene with the risk of developing obesity. It is believed that obestatin Q90L does not sufficiently block ghrelin-induced appetite activity, and therefore the SNV rs4684677 A allele of the GHRL gene contributes to the development of polyphagia [19]. We have demonstrated for the first time that the missense variant of SNV rs4684677 (T>A) located in the third exon of the GHRL gene, which leads to the replacement of a glutamine residue with a leucine residue at position 90 (Gln90Leu) of the preproghrelin molecule, is positively associated with the pro-inflammatory status of obese children.

We did not reveal any relationship between the non-synonymous SNV rs34911341 (C>T) GHRL gene and the markers of metabolic disorders. We showed that the frequency of mutant T alleles of SNV rs34911341 of the GHRL gene was significantly lower in individuals with MUO than the allelic frequency of these polymorphisms among individuals with MHO.

It is known that this genetic variant leads to the replacement of arginine with a glutamine residue at position 51 (Arg51Gln) of the preproghrelin molecule, which prevents the proteolytic cleavage of preproghrelin, and as a result, causes a decrease in the serum level of ghrelin [49]. There is scientific evidence that the T allele of SNV rs34911341 (C>T) of the GHRL gene is a protective factor that prevents the development of T2DM [54].

Thus, in obese children, SNVs rs696217, rs4684677 of the GHRL gene are associated with the level of pro-inflammatory activity and laboratory markers of metabolic disorders (Fig. 1).

The GT genotype SNV rs696217 in obese children is associated with the risk of developing the MUO.

Conclusions

1. Missense variants rs696217, rs4684677 of the GHRL gene in children are associated with the development of obesity and metabolic disorders induced by obesity. The development of the MUO phenotype in children is determined by the T allele of SNV rs696217.

2. SNV rs34911341 of the GHRL gene is associated with the MHO phenotype and prevents the formation of metabolic disorders in children.

3. The TA genotype SNV rs4684677 of the GHRL gene in obese children is associated with a pro-inflammatory status.

4. Variants rs696217 of the GHRL gene are associated with certain features of carbohydrate and lipid metabolism in obese children. Children with the CT genotype SNV rs696217 and the MUO have a higher level of basal hyperinsulinemia and insulin resistance, and those with the MHO have a low level of atherogenicity.

5. Determination of the SNV genotype of the GHRL gene will make it possible to predict the likelihood of obesity and to personalize the development trajectory for various metabolic disorders associated with obesity in children.

References


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Original Researches


34. Rivera-León EA, Llamas-Covarrubias MA, Sánchez-Enriquez S, et al. Leu72Met polymorphism of GHRL gene decreases susceptibility to type...
Актуальність.

Виявлено асоціацію між розвитком ожиріння (МНО) та розвитком метаболічних порушень. Контрольну групу (n = 100) представили 252 пацієнти з ожирінням віком 6–18 років. Основну групу (n = 152) становили діти з метаболічно нездоровим станом.

Результати.

Асоціація з розвитком ожиріння (МНО) була вищою для T-алеля SNV rs696217 гена GHRL у здорових осіб (t = 2,31; p < 0.05) та пацієнтів з ожирінням (t = 2,06; p < 0.05).

Интерпретація результатів.

Асоціації різних фенотипів ожиріння в дітей.

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Authors' contribution. Alexandr Abaturov — conceptualization, methodology, software, validation, formal analysis, investigation, resources, writing — original draft preparation, writing — review and editing, visualization, supervision, project administration, funding acquisition; Anna Nikulina — conceptualization, validation, formal analysis, investigation, resources, data curation, writing — original draft preparation, writing — review and editing, visualization, supervision, funding acquisition.

Абатуро О., Нікуліна А.

Асоціації варіантів гена GHRL із розвитком ожиріння та метаболічних порушень у дітей

Асоціації варіантів гена GHRL з ожирінням та метаболічними порушеннями у дітей

Резюме. Актуальність. Однонуклеотидні варіанти (single nucleotide variant — SNV) гена гре́ліну (GHRL) супроводжу́ються продукцією дефектного протеїну препрогреліну, що може призводити до розвитку ожиріння та метаболічних порушень.

Мета: вивчити асоціації гена SNV GHRL із розвитком різних фенотипів ожиріння у дітей. Матеріали та методи. Обстежено 252 пацієнтів з ожирінням віком 6–18 років. Основну групу (n = 152) становили діти з метаболічно нездоровим станом (МНО). Контрольну групу (n = 100) представили діти з метаболічно здоровим станом (МЗО). У 31 дитинній основній та 21 дитинній контрольній групі проведено повногеномне сексомування (CeGat, Німеччина). Рівень інтерлейкіну (IL-1β) у сироватці крові визначали методами імунохімічної лімінієнсцентного аналізу, IL-6 — методом імуноенфекментного аналізу (Synevo, Україна). Результати. Асоціації з розвитком МНО була вищою для Т-алеля SNV rs696217 гена GHRL у здорових осіб (t = 2,31; p < 0.05) та пацієнтів з ожирінням (t = 2,06; p < 0.05). Генотип GT SNV rs696217 був пов’язаний з інсулинорезистентністю (r = 0,40; p < 0,05) у групі МНО і зворотно корелював з умістом холестерину (r = -0,45) та холестерину ліпопротеїнів низької щільності (r = -0,39).

Ключові слова: гре́лін; аналіз однонуклеотидних варіантів гена; діти; метаболічно нездорове ожиріння; метаболічно здорове ожиріння.