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REVIEW PAPER

Obesity-diabetes-endocrinopathy – the metabolic connection

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ABSTRACT

Introduction and aim. The article outlines the mechanisms of interrelationships between obesity, type 2 diabetes, and certain disorders of the endocrine system. The paper explains how insulin resistance develops, which is a key link between obesity and several related disorders, how hypercortisolemia leads to the development of obesity and glucose intolerance, why thyroid dysfunctions are bidirectionally associated with metabolic disturbances, in what way excessive body weight leads to the hypogonadism in men, or how menopause promotes the development of abdominal obesity, carbohydrate intolerance and, in some cases type 2 diabetes.

Material and methods. Scientific articles were reviewed by searching for information using the online database with scientific articles, including PubMed, Google Scholar and other available scientific databases.

Analysis of the literature. The huge prevalence of obesity, diabetes, and hormonal disorders (e.g., autoimmune thyroid disease, female and male hypogonadism) over the contemporary world together with the serious health consequences of these conditions makes up a specific triangle of metabolic connections, increasingly absorbing the human, organizational and financial resources of health systems.

Conclusion. Recognizing the relationship between the components of this triangle and understanding the risks arising from this phenomenon may allow to effectively reduce its impact on our health.

Keywords. diabetes, endocrinopathy, hypogonadism, insulin resistance, obesity

Introduction

Obesity, often referred to as the tsunami of the 21st century is such closely associated with another pandemic of our time - type 2 diabetes, that many use the term "diabesity" to describe both diseases together. On the other hand, many disorders of the endocrine system, e.g., hypothyroidism that occurs with a frequency of about 5% in women and less often in men, menopause that affects all women after 50 years, or looking wider – all kinds of male and female hypogonadism leading to an increase in body weight and glucose metabolism disturbances.1-5

The etiopathogenetic interconnectedness, the very high prevalence and the serious health and socioeconomic consequences resulting from all these diseases make it possible to connect them in a kind of specific metabolic triangle with an increasing impact on health systems in today's world.

Aim

The paper explains how insulin resistance develops, which is a key link between obesity and several related disorders, how hypercortisolemia leads to the development of obesity and glucose intolerance, why thyroid dysfunctions are bidirectionally associated with metabolic disturbances, in what way excessive body weight leads to the hypogonadism in men, or how menopause promotes the development of abdominal obesity, carbohydrate intolerance and, in some cases type 2 diabetes.

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Material and methods

Scientific articles were reviewed by searching for information using the online database with scientific articles, including PubMed, Google Scholar and other available scientific databases.

Analysis of the literature

Obesity

Obesity is a chronic disease characterized by excessive accumulation of fat mass, increasing the risk of many other diseases, including the cardiovascular, metabolic and cancers. Adipose tissue that accumulates fat based on its morphology can be categorized as white (WAT), brown (BAT), or beige. Depending on the location WAT can be classified as visceral (central, abdominal) and subcutaneous. Moreover, in obesity fat mass can increase ectopically as intrahepatic, epicardial, perivascular, mesenteric, omental, and retroperitoneal. Brown adipose tissue is characterized by its morphology and function, with concentrated mitochondria giving it a characteristic brown appearance. Beige fat represents a class of adipose tissue, in which brown adipocytes appear within classical WAT depots.[1]

Excessive WAT leads to the development or to the progression of many closely related metabolic disorders and diseases such as dyslipidemia, diabetes, asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension, cardiovascular disease, esophageal reflux disease, non-alcoholic fatty liver disease, polycystic ovary syndrome, hypogonadism, infertility, osteoarthritis, cancers (esophagus, small intestine, colon, liver, gallbladder, pancreas, kidneys, breasts, uterine, prostate), depression, stress incontinence.[2,3]

According to the World Health Organization (WHO) obesity is now reaching epidemic proportions, being mainly a result of rapidly changing demographic and socioeconomic conditions. In 2016 1.9 billion adults over the world were overweight (body mass index (BMI) >25 kg/m^2) and 650 million (13% of the total population) were obese (BMI ≥30 kg/m^2). Unfortunately, the problem no longer concerns only adults, but also increasingly touches children and young people. In 2018 year 40 million children before the age of 5 were overweight or obese. Only in Africa the number of overweight children increased by 50% over the last two decades. In Asia in 2018 year every second child before 5 years was overweight or obese. This must result in a further increase in the number of obese adults by 5–15% over the next 10-15 years, which in turn will result in a 100,000 additional events of coronary artery disease.[1,4]

Obesity is most often of primary nature. It means, that it develops under the influence of environmental factors that overlap the underlying genetic background. More than 400 genes that may be involved in excessive accumulation of fat tissue have been described. A genetic predisposition may be result of:

- a single mutation, e.g., of a leptin molecule or its receptor (very rare, leads to the development of extreme obesity),
- chromosomal aberration, e.g., Prader-Willi syndrome (much more common, among the other symptoms unstoppable hunger and huge obesity are observed),
- polymorphisms of many different genes (polygenic obesity, the most common).

An increasing role in the pathophysiology is currently also attributed to epigenetic changes.

Among the environmental factors, the most important are the reduction of physical activity and poor nutrition: hypercaloric meals rich in saturated fats, cholesterol, and simple carbohydrates, but poor in polyunsaturated fatty acids and fiber. Normal composition of the intestinal microflora, which significantly affects the energy balance is also important, and in the case of adverse changes inadequate microbiome may promote the accumulation of body fat.[5] A great role is attributed to proper nutrition during fetal life. Among newborns with low-birth-weight childhood obesity and the cardiovascular diseases later in adulthood are significantly more common.[6]

Secondary obesity may be the result of hormonal disorders, of the effects of certain drugs (phenothiazine derivatives, H1-receptor antagonists, oral contraceptives, antidepressants, antiepileptic drugs, antidiabetic drugs, glucocorticoids, β-blockers) and less often of the other causes.

Obesity – insulin resistance – diabetes mellitus

It has been known for a long time that there is a strong relationship between weight gain and the risk of prediabetes and type 2 diabetes. It has been even estimated that every kilogram more in body weight means increase in a chance of diabetes of 4.5% over 10 years. A one-unit higher BMI (approx. 2.7–3.6 kg) equals the 12.1% higher risk of diabetes.[7] In effect, obesity accounts for about half of the new cases of type 2 diabetes in today's world.[8]

Insulin resistance is the key factor of the pathway from obesity to diabetes. With a high BMI, large, fat-filled adipocytes react less well to insulin and are no longer able to accumulate energy in the form of lipids. Fats therefore begin to accumulate in other organs, where they bring on lipotoxicity, which also contributes a local decrease in insulin sensitivity. In adipose tissue itself, altered adipocytes and accumulating mononuclear cells become a source of many hormones, large amounts of free fatty acids (FFA) and many cytokines and adipokines. Biologically active lipid particles – long-chain acylo-CoA esters (LCACoA) formed from the connection of fatty acid and coenzyme A, diacylglycerols and

ceramides generate insulin resistance in peripheral tissues.[9] Released in excess FFA inhibit glucose uptake, hindering the translocation of glucose transporter 4 (GLUT 4) in skeletal muscles and other organs.[10] In addition, free fatty acids inhibit the secretion of insulin by β-cells worsening glucose metabolism also in that way.[11]

Adipokines and cytokines that increase insulin resistance include leptin, resistin, lipocalin 2, interleukin 6 (IL-6), tumor necrosis factor α (TNFα) and others.

Leptin is a hormone that inhibits appetite and reduces the amount of food absorbed in the digestive tract. Generally, this hormone increases the sensitivity of cells to insulin, however it was proved that in patients with prediabetes there is resistance to leptin action leading to increased insulin levels.[12] In consequence insulin and leptin levels are high in obese patients, and it was demonstrated experimentally that insulin stimulates the production of leptin by the adipose cells.[13] On the contrary, high insulin levels impair the physiological hypothalamic response to leptin for reducing appetite; weight loss improves this response.[14] Thus, overweight and obesity themselves generate weight accumulation leading to a vicious cycle. It was shown that high levels of leptin were associated with decreased insulin sensitivity in prediabetes patients.[15] Under certain physiological conditions, leptin increases insulin sensitivity, thereby confirming the existence of an altered mechanism of action of this protein in patients with prediabetes, obesity or overweight. Such associations have been reported in earlier studies, leading to high level of leptin to be considered a predictor of type 2 diabetes developtment, contrary to all the physiological roles that leptin fulfils in normal weight normoglycemic patients.[12]

Resistin is produced in adipose tissue and by immune cells. It seems that its main physiological role is to maintain glucose levels during starvation. While an increase in insulin resistance (as a result of the increase in gluconeogenesis and glycogenolysis with consequential hyperglicemia) under the influence of this factor was clearly observed in animal studies, this effect in humans has not been unambiguously confirmed.[16]

Lipocalin 2 is a protein derived from adipose tissue and liver involved in the immune response to infection. Many studies point to a relationship between its levels and the intensity of the inflammation that accompanies obesity and insulin resistance. A relationship between the amount of lipocalcin 2 in visceral adipose tissue and the severity of the inflammatory process, serum insulin levels, and Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) has been established in humans.[17]

Interleukin 6 (IL-6) produced by epithelial cells, macrophages, and fibroblasts in adipose tissue and in the immune system reduces the expression of insulin receptors in peripheral tissues and inhibits signal transmission from these receptors. IL-6 restrains adipogenesis and causes a decrease in levels of adiponectin – metabolically beneficial adipokine.[18]

Tumor necrosis factor α (TNFα) is a pro-inflammatory cytokine produced by mononuclear cells in adipose tissue and skeletal muscles. Acting in auto- and paracrine manner it reduces insulin sensitivity mainly by inactivation of insulin receptor-associated insulin receptor substrate 1 (IRS1), inhibition of tyrosine kinase activity and, as a result, by stop the translocation of the GLUT 4 in the cell. The production of TNFα in humans is positively correlated with obesity, insulin levels and insulin resistance.[19]

Reduced insulin sensitivity usually precedes the onset of type 2 diabetes for many years. This is because decrease in insulin sensitivity is initially compensated by a higher secretion of this hormone by pancreatic β-cells. However, it should be kept in mind, that despite apparent normoglycemia, the risk of atherosclerosis during this period is comparable to that of overt diabetes.[20] Later, with the progressive dysfunction of β-cells prediabetes and subsequently diabetes appears. Given the prevalence of obesity all over the world, the number of cases of diabetes, which is currently estimated on 463 million worldwide, with prognosis to almost double by 2030 should be not surprising.[21] Diabetes is the main cause of blindness, chronic renal disease, myocardial infarctions, strokes, and lower limb amputations nowadays.[22] Of course, the number of people with prediabetes is much greater, although more difficult to estimate precisely.

Diabetes treatment requires, first of all, implementation of lifestyle modification – reducing of body weight and increasing physical activity. Loss weight by 5-10% leads to a disproportionately reduction in visceral fat mass, and thereby improve insulin sensitivity with subsequent further metabolic and clinical benefits.[23] Among antidiabetic drugs the first-line medicine - metformin reduces insulin resistance and promotes, albeit to a small extent, weight reduction. Also, the so-called incretin drugs and sodium-glucose co-transporter 2 (SGLT2) inhibitors either do not affect body weight or lead to its decrease, which is sometimes even used for the treatment of obesity (liraglutide, semaglutide). However, many traditional drugs, with insulin among them, cause further weight gain.

Bariatric operations, originally designed to promote weight loss powerfully treat type 2 diabetes, causing remission in most cases, through diverse mechanisms additional to the secondary consequences of weight loss. Large observational studies demonstrated that bariatric (now called "metabolic") surgery is associated with reductions in cardiovascular risk factors, macro- and microvascular diabetes complications, cancer and death. Clinical trials, directly comparing various surgical vs non-surgical interventions for type 2 diabetes, clearly demonstrate the for-

mer to be superior for improvements in glucose control, as well as other metabolic endpoints. The safety profiles of modern laparoscopic bariatric/metabolic operations are similar to those of elective laparoscopic hysterectomy or knee arthroplasty.[24]

Obesity and endocrine disorders (endocrinopathies)

Among the endocrine system disorders that lead to weight gain and predispose to the development of obesity can be mentioned:

- Cushing syndrome
- growth hormone deficiency
- hyperprolactinemia
- thyroid diseases
- alleged hypothyroidism
- insulinoma
- hypogonadism
- polycystic ovary syndrome (PCOS)

Adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent Cushing syndrome are rare diseases. The pituitary tumor, which is responsible for 70% of cases of endogenous hypercortisolemia occurs at a frequency of 30/million. The annual incidence of the adrenal origin disease is 2-5/million. Incomparably more frequently hypercortisolemia is a result of the treatment with glucocorticoids (GCS), which have been broadly used in the therapy of many autoimmune, respiratory, gastrointestinal, and other diseases. In Cushing syndrome, a frequency of hyperglycemia is estimated at 53%, and diabetes in 36% of patients.[25] Excess cortisol and its derivatives affect glucose metabolism in many ways. Activation of GCS receptors present on β-pancreatic cells switch on the genomic mechanisms responsible for inhibition of glucose uptake and a decrease in insulin secretion. Impact of incretin hormones (glucagon-like peptide 1, GLP-1) on β-cells is weakened.[26] The effect of glucocorticoids on insulin-producing cells is important as it enables to increase the production of this hormone in conditions of insulin resistance resulting from hypercortisolemia. However, the most important effect of GCS is the strong anti-insulin activity in the liver, skeletal muscles, and adipose tissue.[27] In muscles and adipose tissue insulin is responsible for glucose uptake and its storage as a glycogen. Insulin also inhibits lipolysis and reduces the release of free fatty acids into the blood. In the liver it inhibits gluconeogenesis and glycogenolysis. These processes are significantly disrupted under conditions of hypercortisolemia. This is a result of the restrain of the insulin receptor signal due to effects on IRS-1, phosphatidylinositol 3 kinase (PI3K) and protein kinase B (PKB).[27] Glucocorticoids also inhibit the activity of the enzyme responsible for glycogen synthesis in the muscles and stimulate proteolysis increasing the amino acid pool, which further interferes with the transmission of the signal from the insulin receptor. Naturally, GCS-induced visceral obesity through the mechanisms already described contributes to insulin resistance with a subsequent hyperglycemia.

European Society of Endocrinology (ESE) recommends that testing for hypercortisolism should not be routinely applied in obesity, but only in patients with clinical suspicion of hypercortisolism and in candidates for bariatric surgery. Also, patients using GCS no need such tests. If hypercortisolism testing is considered a 1 mg overnight dexamethasone suppression test as first screening tool is recommended. In case of positive result as a second line test either 24-h urine cortisol or late-night salivary cortisol should be performed. It is worth remembering that treatment of proven endogenous hypercortisolism is not normalizing BMI in most cases.[28]

Growth hormone deficiency syndrome (GHD) is a set of signs and symptoms resulting from impaired growth hormone secretion by pituitary somatotropic cells. Its incidence among adults is estimated at 37.5-42.5/100,000. The most common causes are pituitary tumors (44%) and craniopharyngiomas (11%), less often GHD occurs after radiotherapy of brain tumors (7%), brain injuries, Sheehan syndrome and is caused by lymphocytic pituitaritis. Growth hormone significantly affects metabolism. It has anabolic and lipolytic properties. Its impact on carbohydrate metabolism is more complex. On the one hand, acting directly, antagonistically to insulin, GH inhibits the transport of glucose to tissues and its oxidation, and intensifies gluconeogenesis in the liver. On the other hand, GH indirectly, through its mediator – insulin-like growth factor-1 (IGF-I) exhibits insulin-like activity.[29]

One of the apparent symptoms of GHD is a change in body composition: central obesity and a decrease in lean body mass, in this in skeletal muscle mass. BMI is usually not apparently altered. The consequences of this body composition modification are insulin resistance, an increase in fasting insulin levels, a higher incidence of type 2 diabetes. Substitution therapy with recombinant human growth hormone (rhGH) initially further reduces insulin sensitivity, but during longer treatment beneficial metabolic effects secondary to reduction in visceral fat begin dominating.[30] In clinical practice testing for IGF1/GH is not routinely applied in obesity and should be performed only in patients with suspected hypopituitarism. If tested a GH-stimulation test should be performed. Growth hormone should not be used to treat obesity in patients with normal GH levels.[28]

Hyperprolactinemia can be caused by a pituitary tumor (prolactinoma), but much more often is of physiological origin and occurs in pregnancy, during breastfeeding, in stressful situations, after exercise or during irritation of the mammary glands. Many medications can also cause elevated prolactin levels. Apart

from the effects of on lactation and gonadal function prolactin have significant clinical implications on metabolism. Association between hyperprolactinemia and insulin resistance as well as with metabolic syndrome has been proved. The likely pathogenesis of weight gain in hyperprolactinemia includes decreased dopaminergic tone, leptin resistance, reduction in adiponectin levels, high hypothalamic pressure, and hypogonadism. It can also lead to increased low-density lipoproteins and triglycerides and reduced high-density lipoproteins levels, which is likely the result of reduced lipoprotein lipase activity. This can lead to further weight gain and increased risk of cardiovascular diseases. Testing for hyperprolactinemia should not be routinely performed in obesity. The finding of high prolactin levels first of all requires the exclusion of pregnancy and other physiological causes of this condition. Only when accompanied by clinical features use of small doses of dopamine receptor agonists (DA) to decrease prolactin secretion can be considered. In case of prolactinoma DA should be used for treatment. Therapy can cause weight loss by improving insulin and leptin sensitivity and the lipid profile.[31]

Thyroid hormones – triiodothyronine (T3) and thyroxine (T4) have great impact on energy balance, as they increase the basal metabolic rate (BMR) by stimulating thermogenesis, affect the food ingestion, as well as influence glucose and lipid metabolism. Hypothyroidism leads to the decrease in BMR and reduces thermogenesis, contributing to increase in body weight. The inverse relationship between free thyroxine (fT4) levels and BMI has been demonstrated, so weight reduction usually is accompanied by normalization of hormonal changes.[32] Free triiodothyronine (fT3) levels in persons with a high BMI are normal or elevated.[33] Heightened T4 to T3 conversion observed in such cases may be considered as a compensatory mechanism to prevent further energy gain. Leptin seems to be the mediator in this process. This hormone is produced in larger amounts in overdeveloped adipose tissue and stimulates deiodination of T4 to T3. Leptin also acts centrally, increasing the secretion of thyrotropin-releasing hormone (TRH) and, consequently, TSH and T3 levels. This mechanism also can be thought of as compensatory, preventing further accumulation of energy in a form of a fat storage. The results of the studies on TSH levels in obese subjects are not entirely conclusive. The increase in TSH, observed in majority of the trials is, inter alia, the result of chronic inflammation associated with the obesity. The cytokines produced in such cases (TNFα, interleukins) inhibit the sodium iodine symporter mRNA expression and consequently the uptake of iodide by thyrocytes, which may trigger a compensatory increase in TSH levels.[34] Inversely, the thyrotropic hormone has been shown to directly stimulate adipocytes to produce leptin through receptors present in adipose tissue.

The relationship between thyroid function and the risk and the course of diabetes has been established for a long time. Epidemiological studies confirm a higher incidence of thyroid dysfunction in patients with diabetes, especially type 1 (up to 31.4% of women) compared to persons without this disease.[35] This relationship is explained by the existence of common genes: *HLA, CTLA-4, PTPN22, FOXP3*, responsible for both the development of type 1 diabetes and autoimmune thyroid disease.[36]

Thyroid dysfunction alters glucose metabolism through several mechanisms. Overproduction of thyroid hormones leads to an increase in the degradation rate and to shortening of the half-life of insulin, as well as inhibits the transition of proinsulin into the active hormone.[37] Intestinal absorption of glucose and its production in the liver (gluconeogenesis) are increased. This is partly due to a greater influx of FFA in conditions of augmented lipolysis caused by catecholamines under the influence of overproduction of thyroid hormones. Growth hormone and glucagon secretion increases.[38,39] All these phenomena lead to the hyperglycemia. In turn, in hypothyroidism hepatic glucose production decreases and insulin requirements go down.[40] On the other hand, resistance to this hormone occurs and glucose utility in peripheral organs is impaired.[41]

The effects of T3 and T4 on glucose metabolism are also the results of their interactions with hormones involved in energy balance regulation. Hyperthyroidism leads to a decrease in leptin levels, while in hypothyroidism usually increase in the production of leptin is seen, although the results of the studies on this subject are not entirely conclusive. Reciprocally, as it was already mentioned, leptin is a factor that increases triiodothyronine levels by the impact on type 1 deiodinase. A similar, but inverse relationship occurs between thyroid function and the ghrelin levels. Reduced levels of this peptide are observed in obesity, type 2 diabetes, as well as in hyperthyroidism, which can be consider as a state of negative energy balance. The return of normal thyroid function usually normalizes ghrelin levels.[35] T3 and T4 also affect glucose metabolism by thermogenesis regulation, acting both at the central level in the hypothalamus and locally stimulating the activity of an uncoupling proteins in the brown adipose tissue.[42,43] In diabetes, especially poorly controlled, a fall in the production of thyroid hormones is observed. This is the result of a reduced TSH response to TRH, as well as suppressed conversion of thyroxine into triiodothyronine.[44] The increased insulin levels resulting from resistance to this hormone lead to an enlarging of the thyroid gland, with a tendency to form nodules.[45]

ESE recommends that all patients with obesity should be tested for thyroid function. Testing should be based on TSH and fT4 measurements. Overt hypothyroidism (elevated TSH and decreased FT4) should be

treated in obesity, but hyperthyrotropinemia (elevated TSH and normal FT4), should not be treated with the aim at reducing body weight. ESE recommends against the use of thyroid hormones to treat obesity in case of normal thyroid function.[28]

Insulinoma although very rare is the most common functioning neuroendocrine tumor of the pancreas and is the main cause of endogenous hyperinsulinemic hypoglycemia. The most common clinical manifestations are neurovegetative and neuroglycopenic symptoms secondary to hypoglycemia. Progressive weight gain is also an important clinical feature, due to the anabolic action of insulin and the need to feed periodically to reduce hypoglycemia. Testing for insulinoma should not be routinely performed in obesity. In patients with high BMI and hypoglycemic symptoms blood glucose, insulin, C-peptide 72-h supervised fast may be useful as a first diagnostic procedure.[28]

Male hypogonadism may be defined as a set of signs and symptoms resulting from abnormal gonadal function including impaired gametogenesis and/or the secretion of gonadal hormones.[46] In men, primary (hypergonadotropic) and secondary (hypogonadotropic) hypogonadism are usually distinguished. The most common cause of the former is Klinefelter syndrome, and a latter are pituitary tumors. Rarely is observed so-called "peripheral" hypogonadism, which is a consequence of gene polymorphism for the androgen receptor.

The relationship between fall in the testosterone levels and the development of obesity is bidirectional, however it seems that the impact of body weight on testosterone is stronger than the reverse relationship. Obesity caused by testosterone deficiency should be understood rather as an excess in visceral fat mass (to a lesser extent subcutaneous fat mass) than increased BMI, because hypogonadism, like GH deficiency, alters body composition. Fat mass grows up and a decrease in lean body mass (including muscle mass) is observed, without a marked change in BMI.

Obesity disturbs pulsating gonadotropin-releasing hormone (GnRH) secretion, and consequently decreases luteinizing hormone (LH) and finally testosterone production. Levels of main binding testosterone protein in circulation – sex hormone-binging globulin (SHBG) are also diminished. The effect of excess body weight on testosterone has for a long time been linked mainly to increased aromatization, but currently this mechanism as a crucial process is questioned. At present a significant role is attributed to leptin, which under the obesity conditions stops stimulating production of the kisspeptin – a protein in the hypothalamus necessary for the GnRH secretion.[47] Furthermore, leptin inhibits stimulating effect of LH on Leydig cells.[48] Testosterone treatment reduces leptin production. This effect is indirect, being a consequence of a fat mass decline, although testosterone also acts directly, what indicates a strong relationship between these hormones in terms of testosterone secretion and fat mass regulation. In addition to leptin, also hyperinsulinemia and increased cytokine production play an important role in the genesis of obesity-related hypogonadism. The negative relationship between pro-inflammatory cytokines and testosterone secretion has been demonstrated.[49] E. g. in older men, even a slight increase in interleukin 2 levels results in a marked inhibition of GnRH secretion and a decrease in LH production.[50] In animal experiments, hypogonadism caused by a high-fat diet was associated with the state of inflammation in the hypothalamus, an increase in the expression of pro-inflammatory cytokines and a decrease in kisspeptin receptor expression.[51] The lack of receptors for insulin, leptin, and androgens on neurons responsible for GnRH production indicates that the regulation of the activity of these neurons is indirect.

Low testosterone levels are associated with a higher risk of type 2 diabetes. Inversely, men suffer from this disease have been shown to have lower testosterone than their healthy counterparts.[52] Both insulin resistance and diabetes are more common in men who are hormonally treated for prostate cancer, as well as after testosterone substitution therapy withdrawn.[53,54] The mechanisms responsible for these associations are of central and peripheral origin. In mice with a knockout of the insulin receptor in the central nervous system decrease in GnRH secretion with the subsequent hypogonadotropic hypogonadism occurs.[55] On the other hand, testosterone deficiency leads to the development of insulin resistance, which is at least in part the result of abnormal androgen receptor function in peripheral organs. It has been found, that one of the causes of this phenomenon is a decreased activity of the α-coactivator of the peroxisome proliferator-activator receptor gamma (PPARγ).[56] Testosterone treatment improves insulin sensitivity, which is associated with an increase in the expression of genes responsible for transmitting the signal from insulin receptor in adipose tissue.[57,58]

According to ESE guidelines in males with clinical features of hypogonadism but not routinely in all obese patients measuring total and free testosterone (or calculated), SHBG, FSH and LH is suggested. Weight loss is considered of most importance to restore normal testosterone secretion in obese patients with hypogonadism. If weight loss cannot be achieved and if clinical and biochemical hypogonadism persists, treatment with testosterone can be considered in individual cases; contra-indications should be considered, and other causes of hypogonadism should have been ruled out. Testosterone should not be used to treat obesity in patients with normal testosterone levels.[28]

Hypogonadism in women can be caused by the functional or organic disorders of the hypothalamus

or pituitary gland, as well as of diseases of the ovaries themselves, such as gonadal agenesis, chromosomal defects, or steroidogenesis disturbances. Irradiation, chemotherapy, autoimmune diseases leading to premature ovarian failure, nutritional deficiencies, injuries, certain medications and, finally, menopause can also cause a deficiency or complete absence of female sex hormones.[59,60]

Estrogens are responsible for the characteristic distribution of adipose tissue in women, that is, in the gluteal and femoral regions. They operate through estrogen receptor 1 and 2 (ER1 and ER2), which are in fact transcription factors regulating the expression of genes that affect metabolic processes. The non-genomic mechanisms involve the activation of receptors present on the surfaces of target cells. Androgens also affect distribution of body fat, but they are responsible for the abdominal type of obesity. Estrogen deficiency creates a state of relative hyperandrogenism, what explains the redistribution of body fat observed in such conditions in women. Obesity due to lack of estrogen, similarly as it is in the case of hypogonadism in men, rather alters body composition (increases and redistributes fat mass, decreases lean body mass) than changes BMI. Reduced SHBG production, related to lack of estrogen, further increases exposure on androgens. On the other hand, intensified aromatization in obese premenopausal women increases estrogen levels, what results in a characteristic female-type distribution of excess body fat. However, after menopause, when overweight is accompanied by a lack of estrogen, abdominal obesity usually dominates, along with its metabolic consequences – insulin resistance, chronic inflammation, lipid disorders and an increased risk of diabetes and cardiovascular diseases.[61]

Estrogens play an important role in regulating of the energy balance. They significantly affect metabolism of the fat tissue. Under conditions of estrogens deficiency mononuclear cells infiltrate fat tissue, the production of pro-inflammatory cytokines increases, and insulin resistance appears, potentiating the cardiometabolic risk. Another important feature of female sex hormones is the "browning" of white body fat. This process, which makes possible to remove excess energy in the form of heat emission, without putting it in high-energy compounds ceases under conditions of scarcity of these hormones.[62] Estrogens inhibit appetite, what can be observed for example during the menstrual cycle, when the amount of food consumed decreases gradually from the follicular phase to the time before ovulation. The mechanisms of action of estrogens in this regard are very complex and involve several processes in the central nervous system and in peripheral organs.

Estrogens easily cross the blood-brain barrier and operate in many regions responsible for appetite control. Their activity within the hypothalamus is particularly important, as they inhibit the expression of neuropeptide Y through ER1 receptors and Gq-coupled membrane-estrogen-receptors.[63] An additional mechanism is the inhibition of production of ghrelin – the strongest orexigenic peptide mainly derived from the stomach.[64] Hence, estrogens deficiency increases appetite and contributes to the accumulation of energy. A relationship between estrogens levels and leptin production and the participation of this hormone in the mechanisms of estrogen-related regulation of energy balance are not clearly established.[65] Estrogens also affect resting energy expenditure (REE). In the absence of these hormones a decrease in REE occurs, and the substitution therapy in women before menopause restores the correct energy balance.[66] In animal studies estrogens also restored energy expenditure associated with physical activity, but this feature has not been confirmed in humans.[67]

Female sex hormones are involved in carbohydrate metabolism. Although skeletal muscle mass in premenopausal women is 2/3 lower and fat mass is 50% higher than in men, the incidence of diabetes is similar for both sexes. The use of estrogens in women with lack of these hormones causes an increase in insulin sensitivity and lowers blood glucose levels. Such effect is observed in both healthy women and diabetics, although of course treatment with estrogens is not enough to cure the disease. Studies using a metabolic clamp are best model to observe the beneficial effects of estrogens on insulin-dependent processes: higher glucose uptake in muscles, inhibition of this sugar production in the liver and suppression of lipolysis in adipose tissue. In this way, they act against the onset of obesity, inhibit the increase in insulin resistance and thus prevent the development of type 2 diabetes. Another action of estrogens includes their impact on pancreatic β-cells. It has been shown in animal studies, that these hormones protect β-cells from the damaging factor (streptozocin) and prolong their survival. There was also a significant gender-dependent difference in the incidence of lipotoxicity, resulting in impaired insulin production by β-beta cells under the influence of a high-fat diet. This phenomenon occurred 28% less frequently in females compared to male rodents, which is explained just by the protective effects of estrogens.[68] Similarly, β-cell glucotoxicity was much less common in females.[69] ESE suggests assessing gonadal function in female patients with menstrual irregularities and chronic anovulation/infertility but not routinely in all females with obesity. For evaluation of menstrual irregularity measuring LH, FSH, total testosterone, SHBG, Δ-4-androstenedione, estradiol, 17-hydroxyprogesterone and prolactin are suggested, ideally during the early follicular phase. Anovulation requires assessing of gonadal function by measuring LH, FSH, estradiol, progesterone and prolactin. ESE does not recommend starting estrogen substitution in post-

menopausal obese women with the sole aim to reduce body weight.[28]

A special group are women with polycystic ovary syndrome (PCOS). This syndrome consists of chronic anovulation, hyperandrogenism and polycystic ovaries and leads itself to the insulin resistance, which is found in up to 75% of patients. The addition of obesity, often of abdominal nature, which affects 30–70% of patients, further decreases sensitivity to insulin and leads to compensatory hyperinsulinemia. High insulin levels stimulate the activity of enzymes responsible for ovarian androgen secretion and reduces the production of SHBG in the liver, which enhances hyperandrogenism. Hyperinsulinemia also inhibits the production of proteins that bind insulin-like growth factors 1 and 2 (IGF-1 and IGF-2), which in free form also contribute to ovarian dysfunction. Moreover, the expression of adipokines (leptin, adiponectin) altered in obesity modulates the activity of the hypothalamic-pituitary-gonadal axis by affecting receptors in the pituitary gland further increasing the production of hormones in the ovaries. Adipokines also directly affect ovarian function, i.e., by stimulating the synthesis of estradiol in follicular cells and progesterone by granular cells. As a result, women with PCOS, in addition to ovulation disturbances and deterioration of reproductive abilities, are at a higher risk of developing type 2 diabetes and other metabolic disorders, which leads to a higher incidence of cardiovascular diseases.

To assess androgen excess when PCOS is considered based on the clinical features. total testosterone, free T, Δ-4-androstenedione and SHBG should be measured. Additionally ovarian morphology and blood glucose should be evaluated. In women with PCOS with metabolic syndrome features metformin treatment is recommended.[28]

The etiopathogenetic relationship between obesity, insulin resistance, diabetes, and some endocrine disorders presented in outline in this paper are strong, usually reciprocal, and include both genomic and non-genomic mechanisms. The huge prevalence of obesity and diabetes as well as increasing occurrence of certain endocrine diseases such as autoimmune thyroiditis all over the world becomes a problem not only medical but also socio-economic, consuming the organizational and financial resources of health systems. Only the cost of treating obesity and its complications was estimated at about $2 trillion in 2014, representing 2.8% of the global domestic product (GDP) of all countries in the world.[70] Expenditures for diabetes and related complications treatment were $825 billion in 2016.[71,72]

Conclusion

Unfortunately, awareness of this problem among patients, and among health professionals is still inadequate, although only understanding the risks arising from the scale of the phenomena and understanding the relationship between diabetes, endocrinology and obesitology will allow to effectively reduce the impact of this specific metabolic triangle on the world population.

Declarations

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Author contributions

Conceptualization, J.K., P.D. and W.Z.; Methodology, J.K., P.D. and W.Z.; Writing – Original Draft Preparation, J.K., P.D. and W.Z.; Writing – Review & Editing, J.K., P.D. and W.Z.

Conflicts of interest

Authors have no conflicts of interest to declare.

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