

# OBESITY ASSOCIATED PATHOLOGY: FREQUENCY, CHARACTER AND SOME MECHANISMS OF FORMATION

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**E.I. Panova**, D.Med.Sc., Professor, the Department of Endocrinology and Internal Diseases<sup>1</sup>;  
**O.V. Martyshina**, Postgraduate, the Department of Endocrinology and Internal Diseases<sup>1</sup>;  
**V.A. Danilov**, Chief<sup>2</sup>

<sup>1</sup>Nizhny Novgorod State Medical Academy, Minin and Pozharsky Square, 10/1, Nizhny Novgorod, Russian Federation, 603005;

<sup>2</sup>Medical and Sanitary Unit, Ministry of the Interior of Russian Federation, Malaya Pokrovskaya St., 12, Nizhny Novgorod, Russian Federation, 603000

There have been considered modern views on the problem of obesity as a widespread disease, which manifests itself as multi-syndrome pathology involving all organs and systems, mostly cardiovascular system. There has been emphasized an unfavorable role of abdomino-visceral (android) obesity as a strong risk factor of cardiovascular pathology and type 2 diabetes mellitus — the diseases that currently are the main causes of lethal outcomes in economically developed countries.

Some mechanisms of organ pathology associated with obesity have been described, in particular, those determined by endocrine function of fat tissue. Unfavorable effects of obesity, chiefly morbid obesity, on respiratory system, gastrointestinal tract, urinary system and musculoskeletal system have been shown.

**Key words:** obesity; cardiovascular complications; adipocytokines; obesity associated pathology.

At present obesity is considered to be a chronic polietiologic disease which manifests itself by an excessive amount of fat tissue and develops under the influence of physiological and genetic as well as environmental factors. In the modern world obesity is recognized as a new “global non-infectious epidemic” on account of high prevalence (up to 30% of adult population) and steady rise of morbidity [1]. According to the WHO’s recent estimation, about half of the population, i.e. over a billion people are overweight, when a body mass index (BMI) is 25–29 kg/m<sup>2</sup>, in industrially developed countries except Japan and China, and over 20% population in the majority of European countries and 25% in the USA have obesity (BMI ≥ 30 kg/m<sup>2</sup>) [2]. Obesity incidence increases steadily, “the rejuvenation” of the contingent being an alarming trend.

As early as 1998 the WHO recognized obesity as a chronic disease which steadily progresses without treatment. The social significance of the problem of obesity is determined by the threat of disability of the working age patients and a decrease in general life expectancy [3–8] because of frequent development of grave concurrent illnesses, primarily such as type 2 diabetes mellitus (2 DM), arterial hypertension (AH), dislipidemia, atherosclerosis and diseases associated with it, sleep apnea syndrome, hyperuricemia, cholelithiasis, gout, malfunction of the reproductive system, diseases of the locomotor system, some oncological diseases (endometrium, cervical, ovarian and breast cancer in women, prostate cancer in men; rectal cancer in both sexes), varicose veins of the lower extremities, hemorrhoids [9].

At present two kinds of obesity are distinguished: android and gynoid, fat patterning in the body for their differentiation being of fundamental importance. From the point of view of the development of a concurrent pathology the abdominal type of obesity (android subtype) is more significant, and the waist circumference (WC) measurement showing primary accumulation of fat in the abdominal area tends to become an indicator of an obesity — related pathology risk. On implementation of computer tomography and magnetic resonance imaging into medical practice the abdominal type of obesity was divided into two subtypes — abdominal visceral and abdominal subcutaneous, it being established that it is abdominal visceral obesity that generally combines with an unfavorable metabolic profile. WC is recognized as the most reliable marker of the risk of developing most of the pathological conditions related to obesity, including an increased risk of death. Men with WC equal to 94–101 cm and women with WC equal to 80–87 cm have proved to have an increased risk and with higher values of WC a high risk of the development of cardio-vascular diseases and 2 DM. Waist-to-hip ratio (WHR) is also an important measure. If the given ratio exceeds 0,95 in men and 0,85 in women, we can already say about pathologic fat deposits in the abdominal region.

Recently obtained data indicates that fat tissue is an active endocrine organ performing auto-, para- and endocrine functions [10–15]. It is known to have receptors of a considerable number of hormones, cytokines the effect of which are being investigated actively at present. Complicated mechanisms of connection between fat tissue

For contacts: Martyshina Olga Vyacheslavovna, phone: +7 910-134-98-83; e-mail: olgamichaleva@mail.ru

and neuroendocrine regulating centers make it possible to speak about adipocytes as cells able to direct or mediated communication with the brain.

In the vast majority of cases obesity is combined with insulin resistance (IR), AH and dislipidemia, forming a so called **metabolic syndrome**. In Russia as well as in other industrial countries among the population over 30 its prevalence, according to some authors' evidence, makes up 10–20% [16, 17]. The clinical significance of disorders and diseases combined within the syndrome lies in the fact that their combination speeds up considerably the development and progression of atherosclerotic vascular diseases which, by the WHO's estimation, are number one cause of death among the population in industrially developed countries [18]. According to G. Reaven's hypothesis, a combination of AH, hypertriglyceridemia, low level of cholesterol (high-density lipoproteins) and glucose tolerance imbalance (up to DM) is not an accidental but natural phenomenon. IR and hyperinsulinemia are the basis for the pathogenesis of metabolic disorder and an independent risk factor in the rapid development of atherosclerosis, and type 2 DM at the exhaustion of insulin reserve [19–21]. The studies have shown that abdominal obesity is closely related to IR and type 2 DM [22].

It has been established that AH in patients with excess body weight irrespective of the type of fat tissue patterning occurs 2.9 times as often as in normal-weight individuals. Thus, a 5% increase in body weight raises a risk for the development of AH by 30% within 4 years [23]. The mechanisms leading to the development of AH at obesity are specific. Substantial role belongs to such mechanisms as IR, that is aggravated against the background of an increase in the level of free fatty acid (FFA), at the same time the latter factor leads to worsening NO secretion with the defect of vasodilatation induced by insulin [24]. IR is associated with the hyperactivation of the sympathetic nervous system, electrolyte imbalance and remodeling of resistive vessels; AH at obesity develops against the background of increased peripheral vascular resistance [25–27]. Obesity considerably affects the structure of the myocardium of the left ventricle even at "soft" AH [28–30]: a higher mass of the left ventricular myocardium is observed (MLVM), the thickness of the posterior wall, interventricular septum and the index of the left ventricular myocardium are increased in comparison with the indexes in patients with AH but without obesity. The end-systolic and end diastolic dimensions of the left ventricle in patients with obesity statistically significantly exceed the values in patients without an excess amount of fat tissue. Such factors associated with obesity in fact as changing rheological properties of blood by rising blood density due to an increase in hematocrit and level of fibrinogen in the plasma [31] contribute to the "afterload" of the left ventricle at increased AP that is considerably conditioned by intensified synthesis in the adipocytes of the PAI-1 factor [32].

The prognosis of AH, particularly in patients with metabolic syndrome is considerably related to a degree of change in the variability of the heart rhythm and the length of a Q-T interval, which depends on the intensity and duration of AH [33, 34]. A link between change in the

variability of the heart rhythm and sudden death as a result of fatal arrhythmia is a proven fact [7, 35], there has been established an influence of obesity on the development of cardiomyopathy and, as a consequence, cardiac failure and sudden death.

Relation between obesity and the development of **ischemic heart disease** (IHD) and an increased risk of death in consequence of such factors as dislipidemia (up to 30% persons with obesity), type 2 DM (89%), AH (about 50%) has been proved [36, 37]. An independent effect of obesity on cardio-vascular system can be explained by its impact on the function and texture of the myocardium, an increase in the cardiac output, development of eccentric hypertrophy of the left ventricle, dystrophic disorders, onset of congestive heart failure. In patients with IHD against the background of gross obesity the combination of the lesion foci conditioned by angiolipomatosis with the foci of cardiosclerosis after old myocardial infarction considerably decreases the functional capabilities of the heart that results in cardiac failure being the primary cause of death. Obesity proper is a cause of cardiac insufficiency in 11% men and 14% women in the USA. Distinct association between obesity and the development of cardiovascular complications and increased mortality was established by the Framingham heart study [38]. Risk of complications and unfavorable outcomes spikes at DM development.

Obesity is a factor aggravating the course of **chronic respiratory diseases** such as bronchial asthma (BA) and obstructive sleep apnea/hypopnea syndrome (OSAH) [35, 39]. According to the epidemiological monitoring, a parallel increase in obesity and BA prevalence among the adult population in industrially developed countries particularly among women is observed [40], which has resulted in a big number of research studies on this problem. Thus, large-scale prospective studies have proved statistically significant connection between obesity and BA in adult population [41]. A few mechanisms of influence of obesity on the development of BA has been shown. It was established that the restrictive character of change in the bronchi at obesity is substantially related to the fat deposit on the diaphragm and interior wall of the chest that results in changing the values of the functions of external respiration. At present the issue of the effect of proinflammatory cytokines of fat tissue on the pathogenesis and course of BA is under active discussion. With obesity the content of such inflammatory mediators as TNF $\alpha$ , C-reactive protein (CRP), IL-6 is known to be increased and the content of anti-inflammatory cytokines is known to be decreased, first of all adiponectin that is accompanied by the aggravation of the inflammation of the respiratory tract and reduction of bronchial patency. Lately the role of leptin as an immunomodulator in the pathogenesis of BA, namely its influence on T lymphocyte proliferation, Th1/Th2 balance, activation and attraction of monocytes and macrophages is also being discussed. Systemic inflammation at obesity is supposed to contribute to allergic inflammation, and a leptinergic signaling pathway is considered as one of the central exocrine mechanisms of pathogenesis of non-atopic BA in adults [42]. It was also established [43, 44] that smooth muscles of the bronchi have receptors to adiponectin, in so doing it,

unlike leptine, does not influence the proliferation of cells of smooth muscles and vascular endothelial growth factor. Research data of one more adipokine in the pathogenesis of BA, namely resistin, have been published. A high level of resistin at BA against the background of obesity directly correlating with the degree of severity of the disease which allows to claim about the role of imbalance of inflammatory mediators, reflecting possible immune mechanisms of the development of obesity and BA. Thus, the conducted research proves that the mechanisms of the development of obesity and BA are interrelated and as a rule it is obesity that becomes a cause of poor control of BA.

A significant problem can be OSAH syndrome. Obesity is one of the most common causes of luminal narrowing of the upper respiratory tract. In patients with BMI more than 29 kg/m<sup>2</sup>, the probability of the development of OSAH is 8–12 times as much as in normal-weight individuals [46]. More than 60% patients with III degree obesity suffer a severe form of OSAH. Prognostically the most unfavorable obesity is abdominal one causing Pickwickian syndrome in a severe case [47, 48].

At present it is considered established [49, 50], that risk factors for cardio-vascular diseases inherent with obesity first of all such as AH and dislipidemy contribute to **renal hemodinamics** disorder resulting in focal segmental glomerulosclerosis (FSGS), chronic latent glomerulonephritis, chronic kidney disease, diabetic and urate nephropathy. It is essential that the development of nephropathy at obesity can be an effect of direct exposure of kidney tissue to the mediators produced by fat tissue such as leptin, TNF $\alpha$ , angiotensin II. Abdominal obesity is an independent risk factor for microalbuminuria [51, 52] and proteinuria [51, 52]. It was previously established [53] that the risk for a stable decrease in glomerular filtration rate up to 60 ml/min in individuals with obesity is higher than in those with normal weight. At examination of patients with massive obesity the presence of marked proteinuria leading to a progressive worsening of kidney function was established. At kidney biopsy glomerulosclerosis and glomerulomegaly is observed in such patients, which can be considered organic impairment of the kidneys at obesity in the absence of other kidney pathologies such as diabetic neuropathy, chronic glomerulonephritis, amyloidosis [54, 55]. However the most commonly occurring morphological form of the lesion of kidney tissue at obesity is FSGS [56], positive correlation between BMI and the level of diurnal proteinuria having been proven.

The studies have established a link between microalbuminuria and an increased level of leptin and endothelin. At that leptin is able to damage kidney tissue by inducing fibrogenesis at the expense of the increase in the expression of receptors to transforming  $\beta$  growth factor. Besides, leptin increases the production of type 1 collagen by these cells and their proliferation as well as the proliferation of smooth muscle cells of kidney vessels, which in its turn contributes to intra-kidney hemodynamics impairment and progression of the deterioration of kidney function at obesity [57]. There has been established a link between the exhaustion of the kidney functional reserve and high levels of iricosuria, homocysteinemia and serum

endothelin-1. Homocysteine is known to be a vigorous mediator of endothelial dysfunction and in combination with hyperuricemia can claim the role of an early marker of the impairment of the kidneys in obesity patients.

With obesity chronic kidney disease at early stages is developed concurrently with the atherosclerotic impairment of carotid arteries which is related to the progression of leptinemia, IR and an increase in evidence of organ-protective characteristics of adiponectin [49, 58].

Multiplicity of organ lesions at obesity, particularly at morbid one manifests itself by high prevalence of the pathology of the **hepatobiliary system**, considerably exceeding that in individuals with no obesity. Thus, according to the autopsy records of patients with type 2 DM against the background of marked obesity the prevalence of non-alcoholic fatty liver diseases reaches 70-93% cases, while the prevalence of the analogous pathology in the adult population is 20–35%, detection of non-alcoholic steatohepatitis at obesity varies from 22 to 37.5%, in 9–10% cases liver cirrhosis is diagnosed [59]. The leading role in the progression of benign fatty liver, the development of non-alcoholic steatohepatitis and liver fibrosis is proved to belong to the phenomenon of lipotoxicity developing under IR, the excessive free fatty acids leading to the activation of lipid peroxidation [60]. At obesity there is a high incidence of the diseases of the biliary tract (64%) [61], such as cholelithiasis (19%), cholesterosis of the gallbladder with the impairment of contractile function (23%), fatty hepatosis (28%), drug-induced hepatitis (14%). It is essential, that up to 19% patients at the age of 45–50 indicate cholecystectomy in past history.

Studying pathology of **the gastro-intestinal tract** at obesity allows detecting common injury of the esophagus, stomach (up to 72%) and the duodenum (66%). The diseases of the pancreas are observed in 18% patients prevailing in women (6:1) [61]. The pathology has a form of chronic (12%) and acute lipogenic (6%) pancreatitis. The endoscopic view at obesity is characterized by atrophic gastritis, sporadic and multiple erosions, sporadic gastric polyps, formation of ulcers of typical localization. The characteristic feature is an insignificant role of *Helicobacter pylori* in ulcerogenesis (12%).

The pathology of the lower part of the gastrointestinal tract is prevalent — that is the pathology of the colon (74%) in the form of intestinal dyskinesia with a constipation syndrome (36%), diverticular disease of colon (28%), polyposis (10%). 39% patients at esophagogastroduodenoscopy show gastroesophageal reflux [62].

Thus, obesity contributes to occurrence and progression of the diseases of all the links of the digestive system and is characterized by homotypic changes among the digestive organs in the form of motor disorders, erosive and in some cases marked atrophic injuries against the background of considerable impairment of microcirculation; common pathology is esophageal leukoplakia or hyperkeratosis, Barrett's syndrome, polyps in the esophagus and adenocarcinoma in some cases.

An alarming fact of a growing number of disabled patients with chronic diseases of the locomotor apparatus against the background of obesity is observed. Recent studies

have proved the involvement of obesity in occurrence and progression of the diseases of the musculoskeletal system, notably the development of osteoarthritis, inflammatory diseases of joints and pain in the lumbar spine that results in the decrease of physical activity and working capacity [63]. Thus, BMI>25 is associated with the increased occurrence of osteoarthritis of knee joints, its radiographic progression is observed at BMI>27.5 and at BMI>35 the occurrence of osteoarthritis is 4 times as much as with normal weight [64]. Some features of osteoarthritis in women depending on obesity and its type are traced in the studies [65, 66]. It was determined that the clinical features in case of android obesity are more marked para-articular tenderness and thickening of the synovial membrane of the knee joints as well as an increased level of total cholesterol and CRP. A strong link between obesity and an increase in replacement frequency of knee and hip joints has been proved. It is essential that obese patients suffer from more postoperative complications after arthroplasties and experience slow and inadequate joint function recovery and more pain. Direct correlation between the intensity of joint pathology and severity of obesity has been established. Thus, at morbid obesity (BMI>40) a far gone (III–IV) radiographic stage of osteoarthritis [66] is observed in the overwhelming majority of cases.

Thus, modern studies give convincing evidence that obesity is a major risk factor for occurrence and progression of multiple organ pathology.

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