The civilization-related phenotypes of abnormal fatty tissue distribution: visceral obesity and sarcopoenic obesity

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Summary

Obesity is a well-known risk factor of abnormal carbohydrate and lipid metabolism, arterial hypertension, and cardiovascular diseases. This risk increases with abnormal fat distribution with excessive fat accumulation in the abdominal cavity, liver, pancreas, heart, kidneys, blood vessels, and muscles. In this review we present pathogenesis, diagnostic challenges and metabolic consequences of visceral and sarcopoenic obesity — the new phenotypes of fat distribution in human evolution.

key words: visceral obesity, sarcopoenia, sarcopoenic obesity

Background

The incidence of obesity systematically increases, which has a significant impact on global mortality rate, financial burden due to incapacity for work, and increased health care costs. It has been estimated that obesity, expressed as the body mass index (BMI) above 25 kg/m^2, affects approximately 37% of men and 38% women of the world population. This, in turn, is related to increasing rates of the diseases that are associated with excess body fat, such as abnormal carbohydrate or lipid metabolism, hypertension and atherosclerosis [1]. However, it is widely accepted that the risk of these metabolic disorders is associated rather with fat distribution than excess body fat *per se*, particularly with new, in the context of human evolution, phenotypes of abnormal fat distribution: visceral obesity and sarcopoenic obesity.

Visceral obesity

Abdominal obesity, composed of excess visceral fat (VF) and excess subcutaneous fat within the abdominal area, is one of the main diagnostic criteria for the metabolic syndrome. Visceral obesity is defined as excessive fat accumulation in the omentum, mesentery, intestine and intra-abdominal organs. High prevalences of visceral obesity are primarily attributed to unfavourable contemporary lifestyle which may be overlapped by genetic and environmental factors. VF is composed of adipocytes which show several morphological and functional differences in comparison with those in the subcutaneous fat.

First, adipocytes in VF are usually hypertrophic, unstable and break easily in response to mechanical or humoral stimulation releasing triglycerides, fatty acids and diacylglycerols into the blood stream [2]. Second, a low expression of the insulin and adrenergic α_2 receptors and high expression of the adrenergic β_3 receptors promotes lipolysis, which contributes to the development of insulin resistance [3]. Third, VF is easily infiltrated by macrophages, resulting in the increased production of interleukins (IL), predominantly IL-6 and IL-8, tumour necrosis factor α (TNFα), macrophage colony stimulating factor (MCSF)

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and other proinflammatory cytokines, which overall induce a low grade chronic immune inflammation. In addition, in the insulin receptor f VF adipocytes the serine phosphorylation and tyrosine dephosphorylation processes are impaired, which may further enhance insulin resistance [4–6] — a key process in the pathogenesis of type 2 diabetes (T2DM). Finally, the glucocorticoid receptors are overexpressed in VF [7]. Glucocorticoids are known to accelerate the differentiation and inhibit proliferation of adipocytes, leading to their hypertrophy [7, 8]. Based on this observation, several concepts linking hyperproliferation of adipocytes in the VF and increased glucocorticoids concentration in response to stress have been developed [9, 10].

Factors initiating visceral fat accumulation

It has been suggested that chronic psychological stress or impaired coping with stress may induce a moderate hypercortisolism and activation of the sympathetic nervous system but with no essential influence on the hypothalamic-pituitary-adrenal axis. Studies showed that in VF there is a high expression of the 11β-hydroxysteroid dehydrogenase type 1 (11βHSD), which is a microsomal enzyme catalysing conversion of cortisone to cortisol. The increased activity of 11βHSD stimulates VF proliferation, especially on high-fat diet [11, 12], which contributes to increases in fat cells size and lipolysis [13]; these processes do not seem to depend on the level of obesity and body composition [14].

Aside from direct glucocorticoid effects, many environmental factors associated mainly with contemporary life style, dietary habits, and comorbidities have been identified and related to visceral obesity (Table I) [13, 15, 17, 18]. Eating food containing processed fructose and saturated fat has been recognized as the strongest dietary factor that increases the

Table I. Risk factors for visceral obesity

Age
Gender (males)
Low testosterone and dehydroepiandrosterone levels (males)
Hyperandrogenism (females)
Polycystic ovary syndrome
Increased activation of endocannabinoid system
Grow hormone deficiency
Excess of egzo- and endogenic glucocorticoids (stress, Cushing disease)
Coexisting autoimmune diseases
Dietary factors: excessive intake of fructose, saturated fatty acids and calories leading to increase in free fatty acids concentrations in plasma
Low physical activity
Impaired quantity and quality of sleep

VF formation, while the Mediterranean diet shows the opposite effect [18]. In a broader sense, all these factors can be considered as potential stressors and therefore they are likely to induce a chronic inflammatory process in a similar way that is observed in conditions with excess of endogenous glucocorticoids.

Assessment of visceral fat

Until recently, computed tomography (CT) and magnetic resonance imaging (MRI) have been the only available techniques to assess VF. However, these techniques are costly, time-consuming or associated with a risk of radiation. Therefore, other imaging techniques have been developed to quantify VF. Of them, dual-energy X-ray absorptiometry (DXA) seems to provide the most promising results. In the standard DXA whole body scan, newly developed application CoreScan® automatically calculates VF by subtracting the abdominal subcutaneous fat from total abdominal fat (Figure 1). Time of this examination is relatively short and patient's irradiation low [19, 20]. DXA-derived VF is well correlated with VF calculated CT ($R^2 = 0.957$) [21].

The main limitation of these imaging techniques in determining the risk of cardiometabolic diseases is the lack of universally accepted cut values for VF mass and volume that makes it unable to define the visceral obesity based on the results of CT, MRI, and DXA measurements. In observational studies, the VF area in the CT scan above 110–130 cm^2 was found as the predictor of cardiovascular disease, dyslipidaemia and insulin resistance [22, 23] but other studies proposed different cut-offs [24]. On the other hand, using the CoreScan application we have recently demonstrated that normal values of VF volume and mass in young healthy women were 250.3 ± 194 cm^3 and 235.9 ± 183 g, respectively [25]; however, these should be confirmed in patients with cardiometabolic diseases. Therefore, there is an urgent need to define the visceral obesity based on the VF cut values above which the risk of T2DM, dyslipidaemia, and cardiovascular diseases is increased.

Opposite to visceral obesity, abdominal obesity is well-defined based on the measurements of waist circumference (WC). Importantly, WC may also be a good surrogate indicator of visceral obesity, because it correlates both with VF mass (R = 0.703) and volume (R = 0.701) determined by DXA [26].

Visceral fat and metabolic disorders

The results of many studies suggest that an excess of VF increases the risk of cardiovascular and metabolic disorders, mainly the conditions that are
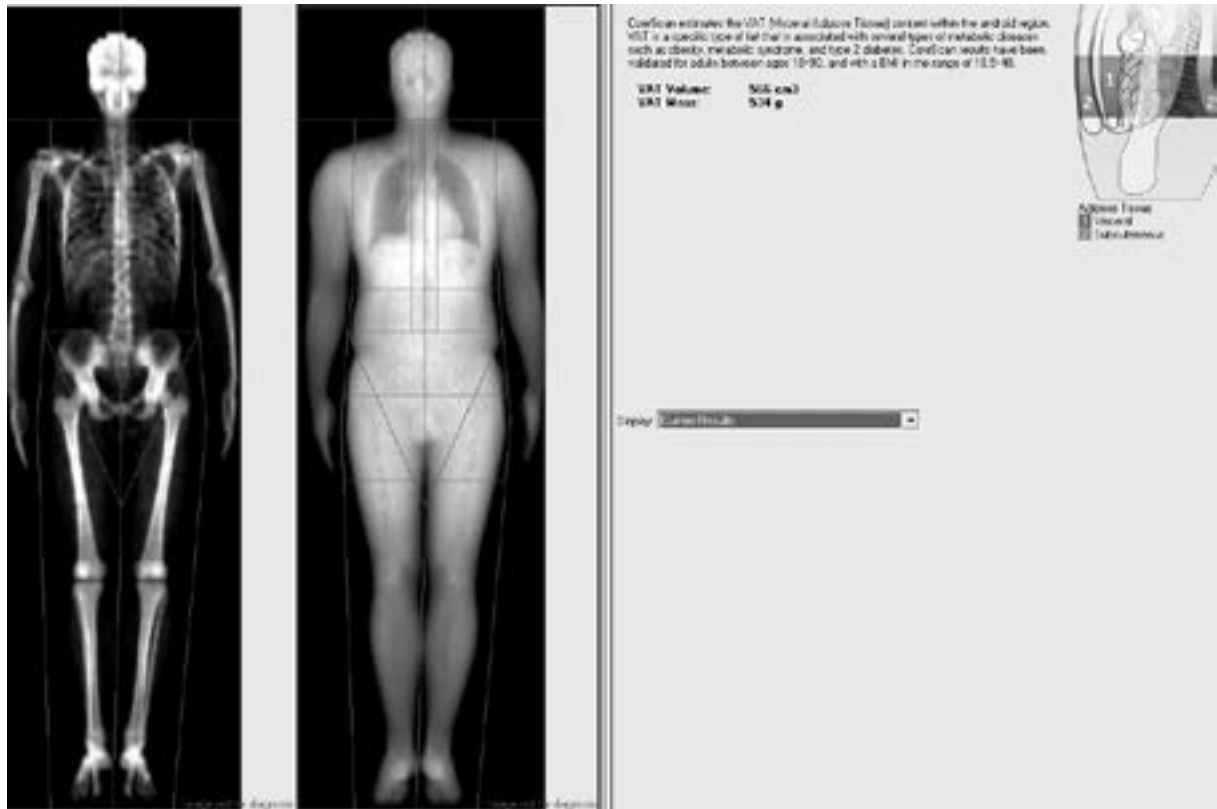
Figure 1. Visceral fat measured by dual-energy X-ray absorptiometry
The image is taken from own database

Table II. Metabolic abnormalities associated with proliferation of visceral fat and extra-abdominal fat depots

Insulin resistance and type 2 diabetes
Atherogenic lipid profiles (↑ triglycerides, ↓ HDL, presence of VLDL)
Coronary heart disease
Heart failure
Hypertension
Metabolic syndrome
Obstructive sleep apnoea
Cancer of the large intestine, oesophagus, breast, prostate
Benign prostatic hyperplasia
Chronic kidney disease
Microalbuminuria
Increased prothrombotic activity in arteries and veins
Sarcopoenia

closely related to a reduced insulin sensitivity (Table II). However, regardless of the method used for assessment, the VF mass, volume, or cross-sectional area are linearly associated with indices of insulin resistance and risks of impaired glucose tolerance and T2DM [27–31]. A crucial role in this process seems to play accumulation of triglycerides and fatty acids in abdominal organs as a result of excessive feeding and increased lipolysis in VF. High concentrations of triglycerides in the blood of the portal vein can accu-

mulate in adjacent organs, initiating non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty pancreas disease (NAPLD).

NAFLD includes a wide range of morphological abnormalities in the organ structure from mild steatosis throughout fibrosis and chronic liver inflammation to cirrhosis and even hepatocellular carcinoma [32]. It is believed that NAFLD is also a strong predictor of impaired glucose homeostasis because as many as 93% of patients with NAFLD and baseline fasting glucose above 89 mg/dl may develop pre-diabetes within seven years [33]. This may apply not only to obese but even to normal weight subjects, particularly in cases with elevated levels of liver enzymes: gamma-glutamyl-transpeptidase and alanine aminotransferase. The latter enzyme was proposed as an early marker of T2DM risk [34]. NAFLD can be a marker of ectopic extra-abdominal fat depots, chronic systemic inflammation, dyslipidaemia, oxidative stress, and cardiovascular disease [35].

In turn, the NAFPD leads to remodelling of the organ structure, which predisposes to acute or chronic inflammation and pancreatic cancer. It has been also suggested that NAFPD, similarly as NAFLD, may be a marker of impaired glucose tolerance and T2DM [36].

Extra-abdominal visceral fat depots

Recently, more attention has been paid to extra-abdominal fat depots (Table III). They can be found in the heart, arterial walls and kidneys. Extra-abdominal depots develop mainly in obese, but can also be identified in overweight or normal weight individuals, particularly in those with excess intra-abdominal fat [37–41].

Adipocytes in fat depots exhibit similar morphological and functional properties as those accumulated in VF. After macrophages infiltration, they secrete pro-inflammatory cytokines into the blood, which induce a low-grade, non-infectious inflammation [41, 42]. In addition, extra-abdominal fat depots may exert unfavourable local effects. In the heart, the adipose tissue can accumulate in cardiomyocytes, epicardium and pericardium [43]. Excessive uptake and oxidation of fatty acids in cardiomyocytes produce lipotoxicity, which predisposes to atrial fibrillation, decreased diastolic compliance of the left ventricle and muscle fibrosis, leading to heart failure [44].

Under physiological conditions, there are small lipid deposits that surround the outer surface of large and small arteries. This perivascular adipose tissue (PVAT) releases adiponectin which increases the bioavailability of nitric oxide and activates the production of hydrogen peroxide. These effects are considered as favourable, because adiponectin likely attenuates the vasoconstrictor effect of circulating catecholamines and leading to the lowering of systemic blood pressure [45]. However, in obese subjects, in the mechanism that has not yet been fully elucidated, the beneficial effect of PVAT is abolished. In obesity, PVAT adipocytes are hypertrophic, similarly like in VF. It has been suggested that hypertrophic PVAT adipocytes induce local hypoxia and oxidative stress, which may contribute to the development of the resistant hypertension [46]. Interestingly, effective bariatric surgery, at least partially, may reverse this process [47].

Clinical studies have shown that visceral obesity is a risk factor for low glomerular filtration rate and the development of chronic kidney disease [48]. Perirenal fat accumulation increases intrarenal pressure and local production of cytokines leading to hyperuricaemia, renal hypertension and microalbuminuria [49, 50]. However, it is not known whether these abnormalities are associated exclusively with primary fat proliferation in the perirenal space or rather are consequences of excess visceral, or total body fat. A particular form of ectopic adipose tissue is fat infiltrating striated muscles, which may contribute to the development of another phenotype of obesity, sarcopoenic obesity.

Sarcopoenia and sarcopoenic obesity

Sarcopoenia is defined as a reduction in mass and overall function of the skeletal muscles. Unfortunately, muscle mass can be assessed by different definitions and methods of measurement (Table IV) [51, 52], quantitative and qualitative surrogate indicators of the muscle function calculated from height, weight and body composition [53], which significantly hinders comparison of the results obtained in studies on the prevalence of sarcopoenia and its metabolic consequences. For example, Batsis *et al.* [54] in unselected population applied 8 commonly used muscle mass indices calculated by one method (DXA). They found that the incidence of sarcopoenic obesity widely varied from 4.4% to 84% in men

Table III. Diagnostic criteria of sarcopoenia

European Working Group on Sarcopoenia in Older People 2010	International Working Group on Sarcopoenia 2011
Low muscle mass and: Low muscle strength or: Low physical performance Recommended methods of evaluation: computed tomography, resonance imaging, DXA, bioelectric impedance analysis	Low muscle mass in conjunction or not with increased fatty tissue and impairment of muscle function Recommended methods of evaluation: DXA

Table IV. Diagnostic criteria of sarcopoenic obesity

Obesity (total body fat)	Sarcopoenia (muscle mass)	Reference
> 27% (M) and > 38% (F) of body weight	5.75 kg/m² (M) and 10.75 kg/m² (F)	Batsis [64]
Two upper quintiles	Three lower quintiles	Zoico [66]
Upper quintile	Lower quintile	Kim [67]

and from 3.6% to 94% in women, depending on the definition used in this study.

Until recently, the term 'sarcopoenia' was addressed almost exclusively to the natural involutive process associated with ageing. Peak muscle mass is achieved between 30 and 40 years of age and declines with aging by about 8% per year to 70 years of age and by 15% in the next few years [55]. Overall, males have higher muscle mass than females. Muscle mass in men decreases gradually with age, while in women the greatest muscle mass loss occurs after menopause. Loss of muscle mass is accompanied by muscle weakness (dynapoenia), but not linearly in either sex [56]. Age-dependent alterations in the quantity and quality of the muscle tissue result from progressive declines in the size, number and contraction abilities of muscle fibres, increased amount of collagen and myostatin in muscles, lowered production of the growth hormone and IGF-1, and impaired nerve conduction. As a result, sarcopoenia leads to depletion in ability to carry out everyday activities, increased risk of falls and fall-related fragility fractures, disability, loss of independence, and increased risk of death [56, 57].

Moreover, recent studies have shown that elderly people with reduced muscle strength and mass are at high risk for metabolic diseases and cardiovascular events. The prevalence of metabolic syndrome in elderly patients with sarcopoenia is 2–3.5 times higher than in population with normal muscle mass [58], even if the waist circumference is within normal range [59]. Moon *et al.* observed that skeletal muscle mass is inversely correlated with the VF area and the risk of the NAFLD [60]. Sarcopoenia is also often associated with insulin resistance and T2DM [61], arterial stiffness [62], hypertension [63], and increased rates of overall mortality [57, 64].

In healthy individuals, the muscle mass and bone mass are maintained in harmonic balance with body weight. This is achieved via bone mechanoreceptors, which are stimulated by gravity and growth factors produced by skeletal muscles. Recent studies have demonstrated that in some obese elderly subjects this adaptive mechanism is impaired and weight gain does not increase muscle mass and strength. This observation led to implementation of a concept of sarcopoenic obesity [65].

Sarcopoenic obesity is defined as the coexistence of sarcopoenia and obesity. It can be seen not only as a consequence of increasing period of life but also as a negative impact modern life style on muscles. However, similarly to sarcopoenia and visceral obesity that yet have not been unequivocally defined, nor in the assessment of sarcopoenic obesity various referent cut points for muscle mass and body fat assessed by different methods (DXA or bioelectric impedance analysis) have been proposed (Table III) [64–67]. Notwithstanding these limitations, the prevalence of obesity in elderly population is estimated at 5–21%, depending on age, sex and ethnicity.

Compared with sarcopoenia, patients with sarcopoenic obesity more frequently suffer from motoric dysfunction, metabolic syndrome, dyslipidaemia, and insulin resistance [61, 68]. The Study of Korea National Health and Nutrition Examination Surveys 2008–2010 showed similar relationship of sarcopoenic obesity with the risk of hypertension. In the general population above 60 years of age with normal BMI and muscle mass, the prevalence of hypertension was 50%; in those with normal BMI and sarcopoenia the risk of hypertension increased 1.5-fold; with BMI above 25 kg/m^2 and normal muscle mass — more than 2-fold; while with BMI above 25 kg/m^2 and sarcopoenia, i.e. in sarcopoenic obesity — even up to 3-fold [63].

Aside from ageing, infiltration of muscles by the adipose tissue and macrophages may play a role in the development of sarcopoenic obesity. There is increasing evidence that sedentary lifestyle, low physical activity and a high-fat diet may induce this process more than advancing age [69, 70]. Moreover, low vitamin D concentration, which is commonly observed in elderly people, appears to exert an additive effect [71]. Infiltration of muscles by the adipose tissue leads not only to sarcopoenia but also increases systemic insulin resistance [70].

The role of subcutaneous fat in the development of visceral obesity and extra-abdominal fat depots

Majority of studies cited in this review had a cross-sectional design. Hence, the associations between independent factors and outcome variables do not necessarily represent causal relationships. The same issue may apply to the causes of extra-abdominal fat depots. However, a growing body of evidence suggests that extra-abdominal fat storage is initiated by excessive calorie intake, which in combination with low energy expenditure, results in the increased deposition of triglycerides in the subcutaneous fat (SAT). Positive energy balance leads to increases in adipocytes size and overfilling with triglycerides of the SAT capacity, resulting in subcutaneous obesity [72], which was previously considered as metabolically neutral. However, new studies have shown that the excess SAT in the abdominal area (particularly

in its deeper layers) increases insulin resistance in the liver and systemic insulin resistance, a 10-year cardiovascular risk assessed by the Framingham Risk Score, plasma saturated fatty acids concentration, and expression of genes that encode inflammatory cytokines production, lipogenesis and lipolysis [73]. When SAT is not capable of storing excess energy substances, it releases fatty acids into the bloodstream, which may accumulate in the liver, pancreas, skeletal muscles and lead to lipodystrophy [74] and lipotoxicity [75, 76]. In this context, when SAT fails to store excess triglycerides, fat depots proliferate in intra- and extra-abdominal sites [76]. This process, as mentioned above, can be also initiated or accelerated by excess of exogenous or endogenous glucocorticoids. Fat depots, accumulated out of the SAT, may exert various local effects and increase systemic insulin resistance. Hence, it can be assumed that extra-abdominal fat plays a similar role in the pathogenesis of metabolic diseases as VF.

In addition, infiltration of skeletal muscles adipocytes and inflammatory cells results in significant alterations in muscle functions. In normal conditions, muscles produce myokines (myonectin, irisin) that regulate the muscle fibre contraction. When infiltration of adipocytes increases, expression of adipomyokines in muscles is also increased. Adipomiokines are proteins (IL-6, IL-8, monocyte chemotactic protein, myostatin, plasminogen activator inhibitor 1, and some growth factors) produced both by myocytes and adipocytes and they exert a competitive activity to the myokines [77]. This positive feedback loop may enhance negative changes in motoric muscle units leading to a further weakening of muscles [76, 77].

In summary, many individuals prone to metabolic diseases appear to show, for a giving weight, a greater propensity to accumulate fat outside of SAT. This characteristic may be a downstream consequence of an 'oversaturation' of subcutaneous fat storage capacity. VF and ectopic fat including muscle fat, despite of its relatively much lower overall mass in comparison to SAT, may exert not only various unfavourable local effects but also enhance systemic insulin resistance. On the other hand, some individuals with so-called normal weight obesity or those who attained extremely high weight remain normoglycaemic and normolypaemic and have normal blood pressure. These individuals usually have low levels of VF and ectopic fat, normal muscle mass but a high subcutaneous fat content.

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