Visceral fat and insulin resistance – what we know?

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One of the most significant challenges of current medicine is the increasing prevalence of obesity worldwide that is accompanied by a wide range of chronic health complications and increased mortality. White adipose tissue actively contributes to metabolic regulation by production of a variety of hormones and cytokines, commonly referred to as adipokines. The spectrum and quantity of adipokines produced by the adipose tissue of obese patients is directly or indirectly involved in much obesity-related pathology (type 2 diabetes mellitus, cardiovascular disease, inflammatory response). One of the underlying mechanisms linking obesity, diabetes, and cardiovascular complications is subclinical inflammation, primarily arising in visceral adipose tissue. Adipocyte size, number and polarization of lymphocytes and infiltrated macrophages are closely related to metabolic and obesity-related diseases. The storage capacity of hypertrophic adipocytes in obese patients is limited. This results in chronic energy overload and leads to increased apoptosis of adipocytes that in turn stimulates the infiltration of visceral adipose tissue by immune cells, in particular macrophages. These cells produce many proinflammatory factors; while the overall production of anti-inflammatory cytokines and adipokines is decreased. The constant release of proinflammatory factors into the circulation then contributes to a subclinical systemic inflammation, which is directly linked to the metabolic and cardiovascular complications of obesity.

Key words: adipose tissue, inflammation, insulin resistance, macrophages, obesity

INTRODUCTION

Overweight and obesity are characterized by excessive fat accumulation in the body with subsequent adverse effects on human health. Obesity constitutes an important metabolic disease associated with the development of insulin resistance, cardiovascular diseases, type 2 diabetes mellitus, some types of cancer and may cause physical diseases. Obesity, especially abdominal obesity, also plays a causative role in the pathogenesis of metabolic syndrome. In 2016, more than 1.9 billion adults were overweight or obese, unfortunately, these numbers are increasing, especially in children.

ADIPOSE TISSUE DYSFUNCTION IN OBESITY

For many years, adipose tissue was only considered a passive source of energy, which also had a thermal-insulation function and provided mechanical protection to the internal organs. Nowadays, adipose tissue is considered an endocrine organ with immune function and it is involved in energy homeostasis regulation and food intake, energy expenditure, and many metabolic processes in the organism. It was recently reported that the inflammation reaction in adipose tissue is an important mechanism to induce insulin resistance (IR) (ref.,). Two basic types of adipose tissue exist, white and brown, which are histologically and functionally differentiated. White adipose tissue is divided into two types: subcutaneous and visceral (intra-abdominal). Subcutaneous adipose tissue is located under the skin and stores approximately 80% of total body fat. This type of adipose tissue is mainly found in the upper (abdominal, subscapular fat) and lower (gluteal-femoral fat) part of the body. Visceral adipose tissue is located around the internal organs and constitutes about 20% of total body fat and it is associated with IR, high blood pressure, high triacylglycerol levels and increased risk of diabetes and cardiovascular diseases. Specificially ectopic fat plays a great role in cardiovascular diseases. Ectopic fat is the storage of triacylglycerols especially in the liver, skeletal muscle, heart and pancreas (pericardial, perivascular, epicardial) and it can interfere with the cellular and organ functions and it is associated with IR and hyperinsulinemia.

The most important part of the adipose tissue is inherent fat cells called adipocytes. Adipose tissue also contains other types of cells e.g. fibroblasts, preadipocytes, immunocompetent cells (macrophages, lymphocytes), endothelial cells. The composition of adipose tissue changes in response to changes in the nutritional status of organisms. Increased triacylglycerol storage in adipocytes leads to adipocyte hypertrophy (increased volumes of adipocytes) and hyperplasia (increasing number of fat cells) which significantly affects their metabolic properties e.g. insulin sensitivity or endocrine function. Adipocytes produce substances collectively termed as adipokines (adipocytokines) which participate in the regulation of glucose and lipid metabolism, insulin sensitivity, energy homeostasis, inflammation, immunity, vascular
function or coagulation\textsuperscript{35}. The main physiological functions of selected substances secreted by adipose tissue are summarized in Table 1.

Excessive fat accumulation in obese patients leads to significant changes in the amount and function of immune cells in adipose tissue\textsuperscript{31}. The amount of macrophages, mastocytes, neutrophils, T-lymphocytes, and B-lymphocytes increase and, conversely, the amount of eosinophils and some subpopulations of T-lymphocytes decrease in obese beings (Fig. 1). These changes are associated with the development of local and systemic inflammation\textsuperscript{32}. Obesity is associated with elevated amounts of macrophages in adipose tissue\textsuperscript{33}. Lean adipose tissue contains fewer than 10\% of macrophages whereas in obese adipose tissue the number of macrophages is increased nearly to 40\% (ref.\textsuperscript{31}). More than 90\% of all macrophages in adipose tissue are localized near apoptic adipocytes. They are mutually interconnected and create syncytia, which trap free radicals of lipid droplets from adipocytes. They typically form multinucleated cells that represent a characteristic morphological feature of chronic inflammation\textsuperscript{34}.

Macrophages are generally classified into two phenotypes: M1 and M2 macrophages\textsuperscript{35}. M1 macrophages are classically activated with a proinflammatory phenotype. The activation of M1 macrophages is mediated through c-Jun N-terminal kinase (JNK) activator protein-1 and nuclear factor-κB (NF-κB) signaling pathways\textsuperscript{3}. M1 macrophages are activated by the proinflammatory cytokine IFN-γ or lipopolysaccharides\textsuperscript{3,36} and secrete proinflammatory factors (TNF-α, IL-1β, IL-6, IL-12, IL-18, and IL-23) resulting in IR (ref.\textsuperscript{21,27,28}). These cytokines have multiple functions, and are important mediators of inflammation in many chronic diseases including obesity and cancer\textsuperscript{39}. Function of M1 macrophages is the phagocytosis and degradation of the residues of dead cells in damaged tissues as well as the elimination of microorganisms. Alternatively activated M2 macrophages are triggered by the Th2 cytokines, IL-4 and IL-13 (ref.\textsuperscript{40}). M2 activation is mediated by the IL-4-induced activation of Janus kinase and activation of signal transducer and activator of transcription signaling\textsuperscript{3}. In M2 activation, several factors are involved such as peroxisome proliferation-activated receptor or enzymes like adenosine monophosphate-activated protein kinase and arginase-1, which blocks the activity of proinflammatory inducible nitric oxide synthase\textsuperscript{41,42}. M2 macrophages have an anti-inflammatory phenotype characterized by low expression of proinflammatory cytokines and high expression of the anti-inflammatory cytokines (IL-10 and TGF-β) and the main function is to contribute to the healing and regeneration of damaged tissues\textsuperscript{3}. Macrophages are capable of producing proinflammatory and anti-inflammatory factors. This is caused by the presence of both proinflammatory CD11c and anti-inflammatory CD206 on the membrane of macrophages which is used to differentiate M2 and M1 type. Macrophages are able to modify their phenotype according to the environment influences\textsuperscript{43}, but the mechanisms involved in this phenotype switch are still not clear.

In obese adipose tissue the composition of immune cells is shifted and causes the inflammatory reactions in adipose tissue. There is a shift from anti-inflammatory M2 macrophages to M1 proinflammatory macrophages in obese individuals\textsuperscript{33,44}. This is caused by increased attraction of circulating monocytes to adipose tissue and their differentiation into M1 cells, leading to an increase in general inflammatory markers\textsuperscript{35}. On the other hand, Fjeldborg’s study in 2014 found the macrophage phenotype changes in obesity with a predominance of M2 and decreasing M1 markers in subcutaneous adipose tissue\textsuperscript{45}. In addition, Zeyda et al. showed that M2 macrophages can produce proinflammatory cytokotines, which could contribute to systemic inflammation and the development of IR (ref.\textsuperscript{46}). These discrepancies are may be caused by several possible reasons. Experimental data are being obtained from the different type of adipose tissue. In most studies, adipose tissue is obtained from subcutaneous depot but in other studies adipose tissue is gained from omental adipose tissue (visceral adipose tissue). Studies have shown that inflammation state determined by release of cytokotines is elevated in visceral adipose tissue than in subcutaneous adipose tissue\textsuperscript{45}. So this could show that the amount or macrophage phenotype differ between these types of adipose tissue. Furthermore, every patient is a special individual so also the sex and the degree of adiposity may play the key role. The last reason of discrepancies concerns the comparison of measured data in mice and humans in experimental studies. The extrapolation of data from mice to humans may be confusing because human monocytes seem to have distinct physiology from mouse monocytes\textsuperscript{49}. The metabolic differences exist between rodents and human beings which can contribute to the difficulty of application mice data into human therapies.

Macrophages are the source of the elevated inflammatory cytokotines and their accumulation in adipose tissue is associated with IR (ref.\textsuperscript{72}). It has been demonstrated that weight reduction is accompanied by decreasing amount of adipose tissue macrophages\textsuperscript{49,50}. The infiltration of adipose tissue by macrophages positively correlated with body mass index, the amount of body fat, adipocyte size, and the expression of proinflammatory markers (TNF-α, IL-1β, IL-6, IL-13, MCP-1) associated with IR in obese patients\textsuperscript{51}. It was shown that adipose tissue macrophages content is higher in visceral adipose tissue than in subcutaneous adipose tissue which agrees with the hypothesis that visceral fat plays more prominent role in IR (ref.\textsuperscript{50}).

The amounts of classically activated M1 macrophages, Th1 CD4\textsuperscript{+} T cells, CD8\textsuperscript{+} T cells, mast cells, B cells, and neutrophils are increased in obese individuals. Obesity decreases the expression of anti-inflammatory factors and increases the expression of the proinflammatory antigens (F4/80, CD11b - integrin alpha M, CD11c - integrin alpha X) and proinflammatory cytokotines (TNF-α, IL-6, inducible nitric oxide synthase) in adipose tissue. In comparison with lean individuals, the levels of TNF-α, IL-6, IL-1β, MCP-1 and PAI-1 are increased mainly in obese visceral fat. The levels of leptin are also increased in obese beings and correlate with the percentage of body
fat. On the other hand, the adiponectin plasma levels are lower in obese individuals. Alternatively, activated M2 macrophages, Th2 CD4+ T cells, regulatory CD4+ cells, eosinophils, and iNKT cells are the dominant immune cells in the adipose tissue of lean individuals. The M2 macrophages express antigens like CD163, CD206, CD209, and CD301 and produce anti-inflammatory cytokines (IL-1Ra, IL-4, IL-10, IL-13) and arginase 1, which suppress the inflammation, maintain insulin sensitivity, and improve insulin signaling with a protective role in obesity-induced IR.

LINKS BETWEEN OBESITY AND SUBCLINICAL INFLAMMATION

According to evidences of studies, inflammation in adipose tissue may play a critical role in the development of obesity-related metabolic dysfunction11,52-54. Inflammation initiates and further contributes to adipose tissue remodeling which includes adipose tissue hypertrophy55, infiltration of adipose tissue by immune cells56, angiogenesis and fibrosis57, oxidative stress58 and hypoxia59. Many clinical studies have dealt with the subclinical inflammation hypothesis in adipose tissue in obese patients21,22,59. Obesity have been already evaluated as a state of chronical inflammation, which is indicated by elevated levels of C-reactive protein (CRP) (ref.60), IL-6 (ref.61), PAI-1 (ref.62), MCP-1 (ref.63) and TNF-α (ref. 64). The adipocytes of obese individuals are continually overloaded by triacylglycerols and subsequently, maximum capacity of adipocytes is constantly exceeded in terms of triacylglycerol storing, leading to their increased apoptosis. This, in turn, stimulates macrophage infiltration in adipose tissue52,65. The interaction between immune cells and adipocytes leads to adipocyte dysfunction with excessive release of proinflammatory factors into the circulation.

Excessive food intake initiates adipocyte hypertrophy

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and hyperplasia resulting in cellular stress in adipocytes; this initiates oxidative stress and inflammatory responses in adipose tissue and amplifies the systemic inflammation response.\textsuperscript{21,66-68} Hyperlipidemia, hyperglycemia, lipolysis, and gluconeogenesis negatively affect the function of mitochondria and initiate oxidative stress.\textsuperscript{21,22} This oxidative stress forms as a result of an imbalance between the productions of reactive oxygen species and anti-oxidative defensive mechanisms against reactive oxygen species in adipose tissue. The adipose tissue of lean individuals expresses antioxidant enzymes (superoxide dismutase-1, catalase, glutathione peroxidase) for the management of reactive oxygen species production and these expressions are suppressed and reduced in the adipose tissue of obese individuals. The stress-signaling JNK, inhibitor of kappa \( \beta \) kinase (IKK-\( \beta \)), and the transcriptional-mediated NF-\( \kappa \)B pathways are involved in the imbalance between reactive oxygen species and antioxidants.\textsuperscript{22,66} The activation of these pathways stimulates the proinflammatory response, significantly contributes to IR development,\textsuperscript{69} and causes oxidative and endoplasmic reticulum stress.\textsuperscript{22} The JNK and NF-\( \kappa \)B pathways decrease the glucose uptake mediated by insulin and insulin signaling, inducing IR (Fig. 2) (ref.\textsuperscript{70}). Moreover, the activation of the NF-\( \kappa \)B pathway may be associated with endothelial dysfunction, leading to the induction of IR; thus, anti-oxidant therapy may prevent the induction of IR (ref.\textsuperscript{22,71}). Some type 2 diabetes mellitus treatments modulated endoplasmic reticulum stress, possibly indicating a new therapeutic target for treating IR (ref.\textsuperscript{22}).

The activation of the proinflammatory state may interfere with the intracellular signal transduction mediated by insulin in several ways, causing systemic IR (ref.\textsuperscript{65,72}). It may lead to decreasing glucose transporter type 4 (GLUT4) and insulin receptor substrate 1 (IRS-1) expression. It may cause the induction of cytokines that sterically block the binding of insulin receptor with IRS-1. It may also initiate the phosphorylation of serine residues on IRS-1 that block the tyrosine phosphorylation of this regulatory protein, negatively affecting the reaction to insulin.\textsuperscript{65} Obesity is associated with the infiltration of macrophages into adipose tissue. Macrophages produce factors that block the action of insulin in adipocytes by reducing GLUT-4 and IRS-1 expression and attenuate in-

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**Fig. 1.** The comparison of substances released by lean vs. obese individuals. (CD – cluster of differentiation, IFN-\( \gamma \) – interferon \( \gamma \), IL – interleukins, iNOS – inducible nitric oxide synthase, MCP-1 – monocyte chemoattractant protein 1, PAI-1 – plasminogen activator inhibitor 1, TGF-\( \beta \) – transforming growth factor beta, Th1 – type 1 T helper cells, Th2 – type 2 T helper cells, Treg cells – regulatory T cells, TNF-\( \alpha \) – tumor necrosis factor alpha)
sulin-stimulated translocation of GLUT-4 on the plasma membrane. Increasing concentrations of the proinflammatory cytokines, TNF-α and IL-6, may affect insulin action by suppressing or interrupting a signal transduction mediated by insulin and distort its anti-inflammatory effect, promoting the inflammation reaction. The first adipose-derived factor suggested representing a link between obesity, inflammation and diabetes was TNF-α. This assumption was confirmed by the later works which showed a positive correlation between increased TNF-α concentration in human adipocytes and degree of obesity, insulin levels and IR. TNF-α together with IL-6 can attenuate IR by sterically preventing the binding of the insulin receptor with IRS-1, increasing lipolysis and levels of free fatty acids in serum. Proinflammatory factors induce activation of mitogen-activated protein kinase and transcription factors (NF-κB) affecting GLUT4 and IRS-1, blocking the action of insulin and cause IR. In many cases, depression and stress lead to weight gain associated with the accumulation of fat cells, where the proinflammatory response is induced by the release of IL-6. Elevated levels of IL-6 in circulation were connected with stress; thus, IL-6 may be responsible for inducing a systemic inflammation reaction. IL-6 has a lipolytic effect with a consequent increase of free fatty acids levels in circulation. IL-6 inhibits insulin signaling cascade leading to the impairment of insulin-induced insulin receptor and IRS-1 phosphorylation. Saturated free fatty acids and lipopolysaccharides bind to the Toll-like receptor 4 and stimulate cytokine production of macrophages and the production of proinflammatory factors thereby modulating the inflammation of adipose tissue which contributes to obesity-associated metabolic complications. Toll-like receptor 4 regulates insulin sensitivity and also inhibits insulin action and signal transduction through serine phosphorylation of IRS-1 and activation of proinflammatory factors and reactive oxygen species. However, the concentrations of circulating free fatty acids do not increase in portion to fat mass and do not predict the development of metabolic syndrome, although many studies suggest the relationship between the release of free fatty acids from adipose tissue and obesity-related disorders.

Fig. 2. Relationships among inflammation, insulin resistance (IR), and stress in adipose tissue.

CONCLUSIONS AND FUTURE DIRECTIONS

Obesity is viewed as a state of systemic, chronic, low-grade inflammation\textsuperscript{31,32}. The inflammation reactions in adipose tissue are causally linked to obesity and the development of IR (ref.\textsuperscript{34}). Long-term, the etiopathogenetic factor of obesity is very important in the formation of metabolic complications including type 2 diabetes mellitus, metabolic syndrome, dysglycemia, dyslipidemia, and hypertension. The combination of these diseases significantly increases cardiovascular morbidity and mortality in obese patients.

Increased subcutaneous adipose tissue is associated with a reduced risk of obesity-induced metabolic dysregulation and enhanced insulin sensitivity, thus the accumulation of subcutaneous adipose tissue (especially in the thighs, hips and buttocks) may be proposed to be protective compared with the harmful consequences of visceral adiposity\textsuperscript{62}. So the mechanisms that determine the size and expandability of subcutaneous adipose tissue may be important targets for future therapy. Deeper understanding how adipose tissue distribution is regulated may lead to novel therapeutic treatments of obesity\textsuperscript{29}.

Obesity is characterized by increasing fat cell numbers and fat cell size\textsuperscript{63}. This fact leads to the unbalance of proinflammatory and anti-inflammatory factors secreted by adipose tissue. Dysregulation of proinflammatory and anti-inflammatory adipokines contributes to the development of metabolic and cardiovascular disorders. It is proved that weight loss improves inflammatory status in obesity and its comorbidities by decreasing numbers of inflammatory factors\textsuperscript{64,65}. In the obese state, adipose tissue is infiltrated by M1 macrophages that release many proinflammatory factors (e.g. TNF-α, IL-6), thus linking obesity, inflammation and IR (ref.\textsuperscript{79}). A shift towards the M2 anti-inflammatory profile may be a protective mechanism to suppress inflammation in obese adipose tissue thus this will open potential pharmacological treatment strategies in metabolic abnormalities associated with obesity.

Many various approaches have been examined to inhibit inflammatory responses by neutralizing the cytokines, chemokines, adhesion molecules or other mediators\textsuperscript{66}. It was shown that plasma levels of inflammatory markers can be reduced by blocking TNF-α and other studies have demonstrated that intervention of TNF-α antagonist results in reduced blood glucose levels and increased adiponectin levels\textsuperscript{77,78}. The inhibition of IKK-β and NF-κB pathways may suppress the activation or production of proinflammatory cytokines. It is important to understand the actions of the signaling pathways through which adipokines control metabolism and try to discover new therapies for diseases related to adipose tissue\textsuperscript{29}. The identification of the mechanisms inducing the inflammation reactions and the analysis of the immune cells involved in this process could contribute to new treatment strategies for metabolic complications of obesity.

It is demonstrated that leptin levels positively correlate with body fat in obese beings and decrease in lean individuals\textsuperscript{89}, numerous clinical trials have been based on the use of recombinant leptin for weight reduction but this has only led to a slight weight reduction\textsuperscript{90}. Nowadays, recombinant leptin is used to treat monogenic obesity caused by leptin mutation that leads to leptin deficiency\textsuperscript{91}. Further research of the mechanisms of adipose tissue released substances may lead to the better understanding of the development of obesity-related metabolic syndrome.

Nowadays, there are many ways to treat obesity. Conservative (non-surgical) approaches or surgical bariatric procedures exist. Conservative treatment is complex therapy including cognitive behavioral therapy, diet therapy and nutritional education, increased physical activity and pharmacotherapy. The aim of modern drug therapy should be to correct the metabolic disorders underlying the development of obesity and associated health complications thus helping the long-term success of reduction mode. At present, only a limited number of medicines is available for the obesity treatment for which a long-term efficiency and safety have been demonstrated in long-term clinical studies. In case of failure of conservative treatment or after a jojo effect after its termination, surgical treatment of obesity can be considered. For a bariatric surgery body mass index value must be over 40, or in the case of serious obesity-related comorbidities at least over 35. Surgical options for obesity treatment have become one of the most basic practices in the last 15 years that offer long-term, permanent and significant weight loss, especially in grave forms of obesity. Bariatric surgery has proven to be the most effective and long-lasting way of treating patients with the second degree of obesity and some with obesity-related disorders or with the third degree of obesity without other comorbidities\textsuperscript{82}.

Although, the best way to mitigate the metabolic complications of obesity are to increase physical activity and reduce body weight and fat mass because it is documented that exercise attenuate obesity induced expression of inflammatory adipokines secretes by white adipose tissue\textsuperscript{93} and overall physical activity has a positive effects on the subclinical inflammation in obesity\textsuperscript{94}. 
Search strategy and selection criteria

Articles and studies were searched using the Web of Science and PubMed databases. Only English papers were reviewed. The search terms used included “adipose tissue”, “adipokines”, “macrophages”, “inflammation in obese patients” and “proinflammatory factors in obese individuals”.

Acknowledgement: This article was derived from a grant (IRP no. 20154) in the Department of Physiology, Ostrava, Czech Republic.

Author contributions: All authors contributed in writing the manuscript and read and approved the final manuscript.

Conflicts of interest statement: The authors declare that they have no competing interests.

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