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Course notes

Involvement of inflammatory cytokines in obesity and its complications

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Introduction

Obesity represents a major social problem, especially in the developed countries, with growing incidence in adults and children, and it is associated with low-grade inflammation in the white adipose tissue (1). According to recent data, there are around 500 million adult obese individuals worldwide. The definition of obesity is based on the body mass index value (BMI), exceeding 30 kg/m^2 (2).

In the epidemiological study PREDATORR performed on 2,681 Romanian subjects, Popa and his collaborators found that obesity was present in 34.70% of the people included in the study group aged 20 to 79 years, while the metabolic syndrome was 38.50%. The abdominal obesity represented 73.90 % whereas the obesity rate adjusted for age and sex was 31.90 %. They concluded that there is a connection between obesity and kidney disease and several cardiometabolic factors (3). In the same study, glucose regulation disorders were detected in 28.1% of the subjects, leading to prediabetes, diagnosed or undiagnosed diabetes mellitus (4).

In contrast with our ancestors' protein-rich diet, nowadays the majority of people have a diet rich in carbohydrates and lipids. These individuals are very likely to gain weight, especially in the case of a sedentary lifestyle, which is also very common in countries with average- and high income (5). This mechanism may contribute to the development of insulin-resistance (6), another population-level problem regarding the increasing incidence of type 2 diabetes. The high-fat calorie consumption as a result of modern diet leads to increased concentration of polyunsaturated fatty acids (PUFA) with higher omega-6:omega-3 ratio, which can be precursors for several mediators, maintaining a chronic inflammatory state (7). This low-grade inflammation can trigger several chronic diseases such as obesity and osteoporosis (8). Recent research data revealed changes in the human brain due to obesity-related

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inflammation, caused by high sugar and fat intake. This kind of diet is preferred by individuals exposed to high levels of stress, probably based on neurochemical modifications induced in the central nervous system (9).

Cytokines are signaling molecules (mostly proteins, peptides) released by different cells, having an important role in immunoregulation, synthesis of blood cells and lymphocyte transformation. Each representative of this large family of molecules (including TNF – tumor necrosis factor) exhibits its effects by being attached to certain target cell receptors. The cytokine family includes several chemotactic molecules which participate to the signal transmission between the cells. Their secretion depends on cytokines that generate inflammation. Chemokines then act selectively on monocytes, lymphocytes and neutrophil leukocytes, the effect of different chemokines on the leukocytes depends on the chemokine receptors on their surface (10).

Several cytokines are secreted by adipocytes; many of these promote inflammation, the phenomenon being also enhanced in obesity due to the increased number of macrophages recruited in the adipose tissue (11).

Main inflammatory and anti-inflammatory markers released in obesity

Classical cytokines secreted in the adipose tissue

Chronic increase in the serum level of several pro-inflammatory cytokines can be observed in obese patients, such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), together with high-sensitive C reactive protein (hs-CRP), a marker of chronic, low grade inflammation (11). Based on some recent research data, hs-CRP has been proved to be a more sensitive marker associated with obesity compared to IL-6 and TNF-α (1).

IL-6, according to a recent study, has been shown to inhibit subcutaneous adipogenesis. Secreted IL-6 presented a negative correlation with subcutaneous adipogenic capacity (12).

Obesity induces changes also in the cytokine secretion in macrophages, increasing the release of pro-inflammatory factors and reducing the anti-inflammatory ones. Infiltration of different T lymphocyte subtypes in the adipose tissue has also been reported (13). Research data are mainly obtained by studies performed on animals, and data obtained from patients are quite limited. Cytotoxic T cells enhance inflammation and insulin resistance in mice, while regulatory T cells have a protective role. The ratio of helper T1/T2 lymphocytes in visceral adipose tissue of obese patients positively correlates with plasma TNF-α, CRP (C reactive protein) and IL-6, known as markers of systemic inflammation (6).

Leptin, responsible for regulation of food intake, is also an immune modulator; it exhibits pro-inflammatory and pro-aggregating effects. Based on evidence obtained from several studies, leptin stimulates the expression of pro-inflammatory cytokines in immune cells (polymorphonuclear neutrophils - PMN, T lymphocytes, monocytes, macrophages), thus contributing to the low-grade inflammation in the adipose tissue. The effect of leptin on PMN is by induction of TNF-α (14). Leptin also decreases the NO (nitric oxide) availability and thus contributes to the development of endothelial dysfunction, which plays a major role in the development of atherogenesis. A negative correlation was found by some researchers between leptin and adiponectin in human subjects (15).

In obesity, increased leptin and decreased adiponectin levels can be observed. Adiponectin has an anti-inflammatory effect and prevents atherosclerosis; its level is gender- and age-related: girls present higher adiponectin levels compared to boys, and its concentration decreases by ageing. Studies performed on obese children indi-

cated an inverse correlation between adiponectin levels and BMI (body mass index). In adult patients, low levels of adiponectin were associated with the incidence of coronary disease and it was suggested to be considered an independent risk factor for the progression of type 2 diabetes (16). Adiponectin has three circulating isoforms based on their molecular weight (low, medium and high), the last one being considered to be a better metabolic marker than total adiponectin (17).

Recently discovered cytokines released by the adipose tissue

A new marker is, for example, resistin, also known as ADSF (adipose tissue-specific secretory factor), a recently described adipokine, belonging to the family of cysteine-rich proteins, containing 108 amino acids in its active form. Resistin links obesity to diabetes, it contributes to the development of insulin resistance, but several studies suggested its role as a modulator in inflammatory and autoimmune diseases, and also in the development of atherosclerosis (18).

Omentin is an adipokine discovered recently and it is secreted selectively in the visceral omental adipose tissue. Its concentration is decreased in overweight and obese patients having an impaired glucose regulation, in patients suffering from diabetes type 1 and 2, and in patients with polycystic ovary syndrome. Obesity and leptin, insulin and glucose possibly regulate serum omentin levels (19). According to recent scientific data, low values of circulating omentin concentration can be in relationship with excessive deposits of visceral fat and with increased incidence of myocardial ischemia. Thus this substance is suggested as a potential biomarker of metabolic and cardiovascular disorders (20). Other studies revelead that high levels of plasma omentin are associated with improvement of ischemic heart injury and myocardial function after reperfusion in patients suffering from acute myocardial infarction. Studies on mice and on cultured cardiomyocytes showed that omentin suppresses myocyte apoptosis by enhancing the phosphorylation of certain enzymes (21). Significant increase could be observed in serum omentin concentration during weigh loss, this biomarker seems to be closely related to lipid metabolism (22).

Vaspin is a recently discovered adypokine, an enzyme inhibitor acting on the serine protease family, being a predictor of cardiovascular diseases, playing a connective role between overweight and carbohydrate metabolism disorders (23).

Apelin is an adipokine, but it is also secreted in many tissues including the heart, lung and brain, where it acts as a neurotransmitter (24). It influences the cardiovascular system, decreases blood pressure by causing vasodilation using a prostanoid-dependent mechanism, has a positive inotropic effect on the heart muscle (25). Recently it has been proven that it is an adipokine with higher plasma concentrations in obese patients and in type 2 diabetes. Studies suggest its role in the pathogenesis of diabetes (26). Apelin plays a role in the regulation of glucose homeostasis, has an impact also on lipid metabolism (27), energetic and nutritional status, inhibiting insulin secretion (28).

Another cytokine called chemerin showed higher concentration in elderly people compared to younger subjects and in overweight patients compared to those with normal BMI, all of these suffering from PCOS (polycystic ovary syndrome) (29, 30). Chemerin plays an important role in adipogenesis and energy metabolism, it is involved in the development of obesity, type 2 diabetes, metabolic syndrome and cardiovascular pathology (31). Chemerin acts as a stimulating factor for leukocyte migration to the areas affected by inflammation, such as at the level of the joints, enhancing the pro-inflammatory signalling in chondrocytes (32).

IL-8 is an inflammatory cytokine (33), an adypokine showing significantly higher serum levels in patients with obesity compared to a group of patients with normal body weight (34). IL-8 is a mediator having a major role in progression and spreading of head and neck squamous cell carcinoma (35).

Cathepsin-S is a proteolytic enzyme containing cysteine residue in its active site, it has subclasses (S, L, K), the first subgroup is mostly related to the metabolism of adipocytes. Experimental data suggest that the inhibition of this enzyme could decrease the cardiovascular risk and improve metabolism in obese indiviuals (36).

In patients with weight excess, the adipose tissue releases factors which enhance angiogenesis. Data in the medical literature show that the vascular endothelial growth factor A (VEGF-A), which is generated by the intensified production of hormonal compounds and cytokines released by the adipose tissue, plays a central role in the formation of new vessels. Interactions mediated by this growth factor between endothelial cells and pancreatic beta-cells play an important role in the regeneration and differentiation of these endocrine cells (37). The VEGF-A molecule might become a target in future treatment of insulin resistance, obesity and related disorders (Elias I).

Granulocyte-colony stimulating factor (G-CSF) has a metabolic effect that resembles leptin and ciliary neurotrophic factor (CNTF), these substances having a major role in the energetics of the body. G-CSF is also an immune-modulator. In animal experiments on obese mice, G-CSF proved to help the weight loss and protected the heart from obesity-related impairment (38, 39,40). G-CSF induces mobilization and recruitment of neutrophils. G-CSF and also IL-6 are very likely to promote the expansion of myeloid-derived suppressor cells, which migh cause interferences with T cell activation and anti-tumor responses (41).

IL-1β (interleukin 1 beta) is a key mediator of the inflammatory response. It has been demonstrated that by enhancing inflammation at the level of the adipose tissue and by limiting fat expandability, IL-1β contributes to ectopic fat accumulation in hepatocytes and in the macrophages present in the fat-tissue, leading to compromised fat-liver crosstalk in nutritional obesity (42). IL-1β is overproduced in obese patients by leucocytes. It binds to the IL-1 receptor and induces inflammatory gene expression. Inhibition of insulin signaling routes is caused by IL-1β phosphorylation of insulin-receptor substrate 1 (IRS1) (43). Animal studies revealed that lack of IL-1β, its receptor or NLRP3 inflammasome components are protective against the development of adipose tissue inflammation, furthermore, in type 2 diabetic patients the blockade of IL-1 mediated signaling improved glycemic control and reduced markers of systemic inflammation (43, 44).

RBP4 (Retinol Binding Protein 4) is a 21 kDa protein secreted by the liver cells and also by adipocytes and macrophages (45). It plays an important role in the regulation of glucose homeostasis. Animal experiments showed that expression of the RBP4 protein is inversely related to the number of type 4 glucose transporters, and in humans increased RBP4 levels are related to metabolic syndrome (46). RBP4 is also involved in the etiology of cardiovascular diseases. Experiments made on animals revealed that RBP4 contributes to the development of insulin resistance (47) and studies performed on humans confirmed this effect (45).

IL-18 has also been suggested to be produced by adipocytes, it has a pro-inflammatory effect, and its concentration increases in obese subjects. In animal experiments, high levels of IL-18 could be linked to aggravation of insulin resistance (48). A surprising discovery was that IL-18 in obesity and metabolic syndrome is a strong counteracting factor. Animal studies re-

vealed that mice lacking IL-18 or IL-18R have developed obesity, insulin resistance, metabolic syndrome and by administration of recombinant IL-18 these processes are hindered, but the mechanism of this pathway or pathways is still unknown (43). Recent studies revealed that IL-18 is activated by Caspase-1 in inflammosome complexes and acts against obesity. Researchers observed in experiments on mice that animals lacking the NLRP1 inflammosome develop obesity spontaneously, just like those with IL-18 deficiency. Fat accumulation is increased especially in animals receiving a lipid- or protein-rich diet. It has been proved that mice having an activating mutation in NLRP1 leading to increased levels of IL-18 have reduced adiposity and show resistance to food-induced metabolic syndrome (49). Further studies are necessary to clarify the detailed mechanisms explaining the controversial metabolic effects of IL-18.

PAI-1 (plasminogen activator inhibitor type 1) is a glycoprotein produced by hepatocytes, endothelium cells and adipocytes. Its level is increased in insulin resistance and obesity. PAI-1 also acts as a cytokine modulator, regulating the expression of certain inflammatory factors such as IL-8 and leukotriene B4 (50). Plasmatic coagulation-related proteins, such as fibrinogen, PAI-1 and several inflammatory cytokines, such as TNF-α**,** IL-1β, IL-6 are increased in obese individuals due to persistent chronic inflammation (51). Nutritional factors, like free fatty acids (FFA), possess a regulatory effect on PAI-1 expression in macrophages. In raised concentrations of FFA in the bloodstream, an increase of PAI-1 gene expression in adipose tissue and adipose macrophages raised the concentration of circulating PAI-1 and higher PAI-1 protein production can be observed (52). Adipose cell size and adipose tissue mass are in positive correlation with circulating PAI-1 levels. The subcutaneous fatty tissue has a smaller contribution to the production of PAI-1 compared to the visceral adipose tissue. Insulin, glucocorticoids, angiotensin II, TNFα and TGF-β can up-regulate PAI-1 synthesis. Animal studies stated that in mice lacking PAI-1 gene, insulin resistance and obesity development was completely prevented by diet containing a high concentration of fat and carbohydrates (51).

Visfatin is released by many cell types, such as hepatocytes, muscle cells, bone marrow and it is also secreted by the adipose tissue, and its expression is related to obesity. A recent study showed a positive correlation between serum visfatin concentration and other inflammatory markers, such as CRP and IL-6 (53). Visfatin level is also correlated with fasting glucose, BMI and serum triglyceride concentration (54). The pathomechanism of visfatin effect is not completely clarified. Initially, an insulin-like effect was suggested due to its binding to the insulin receptor, but later this mechanism was not confirmed. A study on mouse pancreatic beta-cells revealed that visfatin changed the m-RNA (messanger ribonucleic acid) expression of some diabetes-related genes, including up-regulation of insulin secretion (55). Several studies reported elevated visfatin levels in obesity-related diseases, such as low-grade inflammation, type 2 diabetes mellitus, metabolic syndrome, cardiovascular diseases. In obese individuals, visfatin is secreted especially by the macrophages present in the visceral adipose tissue (56).

A recent study exposed that visfatin significantly increased at the transcript level the expression of the genes for several inflammatory markers such as IL-6 and that of two CXC-cytokines (CXCL2, chemokine ligand 2 and CXCL8 chemokine ligand 8). The upregulation of the secretion of these two CXC-cytokines in a dose and time-dependent manner could also be observed. By investigating the interaction of visfatin-treated endothelial cells with leukocytes a significant increase in the adhesion to monocytes compared to endothelium cells not-treated with

visfatin was shown. The suggested mechanism for these findings could be the upregulation of some adhesion marker expressions, such as E-Selectin, VCAM-1 and ICAM-1 (57).

ANGPTL2 (Angiopoietin-related peptide 2) has been recently described as an inflammatory cytokine released by the adipocytes which promote insulin resistance. Its serum concentration is positively correlated with the development of type 2 diabetes in human subjects (58). ANGPTL2 is involved in several age-related systemic diseases, it is also expressed in the eyes, and it is suggested to be involved in the regulation of choroid neovascularization which leads to macular degeneration (59).

SFRP5 (**Secreted frizzled-related protein 5)** is an anti-inflammatory cytokine, which is involved in glucose homeostasis, increasing insulin sensitivity. Recent studies revealed that it diminishes cardiac inflammation and exhibits a protective effect for the myocardium in ischemia-reperfusion injury (60).

Pathological aspects

Besides obesity and atherosclerosis, mild chronic inflammation occurs in many diseases affecting large groups of population worldwide, such as osteoarthritis, metabolic syndrome, diabetes, gallbladder disorders, non-alcoholic fatty liver disease (NAFLD) and some forms of cancer (2).

Involvement of obesity-related cytokines in joint diseases

Obesity is associated with rheumatoid arthritis (RA) due to the fact that in the fatty tissue a chronic inflammation occurs that may trigger a chronic systemic inflammation, thus, obese patients suffering from RA have more severe disease activity parameters, higher serum leptin levels and laboratory indices, and worse functional outcomes (61).

The metabolic pathways leading to osteoarthritis (OA) in overweight patients (BMI>30) are not completely known, although aberrant adipokine expression is thought to be involved, leading to joint tissue, cartilage, synovium and bone damage. Leptin and adiponectin receptors are expressed on the surface of chondrocytes, synoviocytes and subchondral osteoblasts, their levels are significantly elevated in patients with OA (62). A close relationship has been found between circulating adiponectin concentration and radiographic signs of rheumatoid arthritis in studied patient groups. Adiponectin very likely plays a role in the development of synovial inflammation in patients suffering from rheumatoid arthritis by stimulating the production of certain eicosanoids such as prostaglandin E_2, interleukine 6 and 8 (63). Leptin receptors expressed on chondrocytes induce the synthesis of nitric oxide (NO), pro-inflammatory cytokines and matrix metalloproteinases that lead to cartilage destruction (64). Mechanoreceptors in the joint detect and convert the mechanical joint stress forces into intracellular signals that result in overexpression of prostaglandins, cytokines and chemokines (65). Reactive oxygen species are very likely to play an important role in this signaling (66). Studies on bovine cartilage showed that adiponectin (with and without synergic interaction with interleukine-1) induced collagene release from the cartilage, up-regulated proteolytic enzymes. Adiponectin's contribution to inflammation and degeneration of the cartilage explains the relationship between fat excess and ostheoarthritis (67).

A recent study revealed the differences in subcutaneous abdominal adipose tissue (SAAT) secretory activity between RA and OA patients. In RA, characterized by high-grade systemic inflammation, SAAT may contribute to cachexia, amyloidosis or development of cardiovascular diseases. In OA, characterized by low-grade systemic inflammation, adipokines released by the

SAAT might play a role in the regulation of the intensity of systemic inflammation (68).

Insulin resistance might have a negative impact on the joint tissue, because of a local and a systemic effect. The local effect is due to insulin resistance of synovial membrane in diabetic patients, and the systemic effect derives from the state of a general low-grade inflammation related to obesity and insulin resistance (69).

The role of inflammation and oxidative stress in metabolic syndrome and diabetes mellitus

According to recent research data, inflammation of the adipose tissue has been described in association with metabolic syndrome (MS), this process being characterized by increased cytokine production and monocyte infiltration. Significant elevation of plasma CRP was described in obese patients compared to normal weight subjects, and also in the obese patients with MS compared to those without MS (70). Other inflammatory cytokines, such as TNFα, IL-6 and IL-18 showed increased concentration only in obese subjects with MS. Oxidated LDL particles (Ox-LDL) have been measured to determine the level of oxidative stress, and were elevated in both obese groups, especially in those with MS. Based on the previously presented research data, we can assert that inflammation and increased oxidative stress could contribute to the development of MS (71). Another study described higher resistin levels in patients presenting MS compared to those without this pathology (72).

Oxidative stress can be evaluated by measuring the activity of antioxidant enzymes such as superoxide dismutase or glutathione peroxidase (73). Malondialdehyde (MDA) is another widely used marker of oxidative stress, it is increased in obesity and complications related to it (73). The majority of procedures are based on the MDA-thiobarbituric acid reaction. MDA reacts with the DNA (deoxyribonucleic acid), causes mutations, and forms deoxyguanosine adduct (dGA), which presents significantly lower concentration in individuals doing moderate or intense physical activity (74). Plasma lipid peroxidation level, determined by thibarbituric acid reactive substances (TBARS) was significantly higher in obese, diabetic, and obese–diabetic patients compared to control subjects (75). A seasonal variation can be observed in the metabolic control of diabetic patients, the suggested mechanism seems to be related to weight variation due to changes in physical activity and food intake during different seasons (76).

Obesity and non-alcoholic fatty liver disease

Insulin resistance is an important underlying factor of non-alcoholic fatty liver disease, diabetes mellitus and cancer types in both normal weight and obese patients. Insulin resistant states can predict cardiometabolic disorders; insulin sensitivity evaluation could be beneficial especially in middle-aged subjects in order to identify those presenting a high risk of developing metabolic syndrome (77). Oxidative stress plays a major role in the development of the non-alcoholic fatty liver disease (73).

White adipose tissue (WAT) and brown adipose tissue (BAT) are the two distinct forms of adipose tissues. Initially scientists thought that BAT disappears after birth, but in fact, it is also present, in smaller amounts, in adults and its role is related to thermogenesis. Brown adipose tissue activity is in negative correlation with the BMI and its loss of activity may be related to WAT accumulation (78).

Adipose tissue inflammation, enhanced by IL-1β, is now a well-recognized manifestation of obesity. This mediator also contributes to ectopic fat accumulation. IL-1β proved to have a major contribution to the communication dysfunction between adipocytes and liver cells, leading to insulin resistance of hepatocytes and steatosis (42).

Obesity-related cytokines in cardiac diseases

Obesity is present in around 80% of the patients suffering from type 2 diabetes mellitus and is considered to be an independent risk factor for cardiovascular disease, its evaluation and treatment in these patients is extremely important. In a recent study performed on diabetic subjects, more male and female patients in the high-risk group for CHD had elevated BMI values than those included in the low-risk one (79).

An association has been observed between plasma resistin concentration and inflammatory chemokines such as monocyte chemoattractant protein 1 in non-diabetic adults with cardiovascular diseases (72).

Coronary heart disease (CHD) is a very common pathological condition. Multiple sources linked CHD to obesity. Several obesity-related cytokines are involved in cardiac diseases. IL-6 is a pro-atherogenic cytokine, and it may be a predictor of myocardial infarction risk (80).

TNF-α in animal models can have harmful effects on the cardiac muscle, depending on the cytokine amount and the exposure length. Neutralization of this cytokine led to attenuation of cardiac muscle damage after a cardiac event in mice (81).

Leptin has an important role in cardiovascular diseases. Leptin-deficiency can lead to increased mortality in viral myocarditis (82), higher cardiac remodeling grade induced by chronic ischaemia in different animal models (83).

Adiponectin has an important role in fatty acid catabolism and regulation of serum glucose level (84). Adiponectin concentration decreases in obesity and it is highly down-regulated in obese patients (85). Low serum levels of adiponectin can lead to coronary artery disease, hypertension and a greater risk of myocardial infarction (86). Adiponectin is a protective factor of cardiac myocytes, and adiponectin-deficient mice have shown a worse prognosis in different cardiovascular disease models. The protective effect of adiponectin in ischemia-reperfusion injury proved to be related to reduction of oxidative/nitrative stress (87).

According to recent studies, carotid intima-media thickness is positively associated with the RBP4 concentration (88). The level of this cytokine is related to an increased risk for developing cardiovascular diseases, and it may be a subclinical marker of atherosclerosis (89).

Investigating the role of cytokines in atherosclerosis, ANGPTL2 was found to enhance vascular inflammation by increasing macrophage infiltration and by activation of pro-inflammatory signalling in endothelial cells, causing endothelial dysfunction and progression of atherosclerosis (90).

In obese patients, a paradoxical phenomenon was described. According to numerous studies, the negative impact of obesity on most of the cardiovascular diseases has been shown. Despite the deleterious effect of obesity, recent studies have demonstrated the obesity paradox. Overweight patients and obese patients with cardiovascular diseases presented a better prognosis compared to patients with a normal body weight (91). The metabolic background of this paradox should be further investigated.

Conclusions

Cytokines released by the adipose tissue play a central role in obesity-related complications. Their main source is represented by adipocytes especially by the large white adipocytes located in visceral adiposity, and infiltrated macrophages, the majority of them exhibiting a pro-inflammatory effect. This pro-inflammatory status, maintained by increased levels of these bioactive molecules, represents a risk factor in the development and evolution of chronic diseases, be-

ing involved in the occurrence of several major complications of the background disease.

Further studies are necessary to clarify all the details regarding the pathomechanisms of certain adipokines. Gathering new research data is crucial in this domain, because several cytokines (such as VEGF-A, IL-1β) can be therapeutic targets in the treatment of obesity-related complications.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Abbreviations

ADSF: adipose tissue-specific secretory factor
ANGPTL2: angiopoietin-related peptide 2
BMI: body mass index
BAT: brown adipose tissue
CHD: Coronary heart disease
CL: chemokine ligand
CNTF: ciliary neurotrophic factor
CRP: C reactive protein
CXC: two cysteines separated by an amino acid
DNA: deoxyribonucleic acid
dGA: deoxyguanosine adduct
G-CSF: Granulocyte-colony stimulating factor
11 β-HSD: 11 beta-hydroxysteroid-dehydrogenase (cortisone reductase)
HGF: hepatocyte growth factor
hs-CRP: high-sensitive C reactive protein
ICAM: intercellular adhesion molecule
IL: interleukin
MCP 1: monocyte chemoattractant protein 1
MDA: malondialdehyde
MS: metabolic syndrome
NAFLD: non-alcoholic fatty liver disease
NLPR3: NLR Family Pyrine Domain Containing 3
NO: nitric oxide
OA: osteoarthritis
PAI-1: plasminogen activator inhibitor type 1
PCOS: polycystic ovary syndrome
PMN: polymporphonuclear leukocytes (neutrophils)
PUFA: polyunsaturated fatty acids
RA: rheumatoid arthritis
RBP4: Retinol Binding Protein 4
SAAT: subcutaneous abdominal adipose tissue
SFRP5: secreted frizzled-related protein 5
TBARS: thiobarbituric acid reactive substances
TNF: tumor necrosis factor
VCAM: vascular cell adhesion molecule
VEGF-A: vascular endothelial growth factor A
WAT: white adipose tissue

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