Pro-Inflammatory Profile of Adipokines in Obesity

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Obesity is a disease which leads to the development of many other disorders. Excessive accumulation of lipids in adipose tissue (AT) leads to metabolic changes, including hypertrophy of adipocytes, macrophage migration, changes in the composition of immune cells, and impaired secretion of adipokines. Adipokines are cytokines produced by AT and greatly influence human health.

Keywords: obesity ; adipokines ; chronic kidney disease ; cardiovascular risk

1. Obesity-Induced Changes in Adipose Tissue

Obesity is characterized by an increase in and dysregulation of white adipose tissue (WAT), especially visceral fat, which is associated with altered adipokine secretion. When the threshold of adipocyte storage capacity for fatty acids is exceeded, the processes of hypertrophy and hyperplasia take place [1]. An increased size of fat cells (hypertrophy) and their increased number (hyperplasia) differ in the way they affect the organism. Hypertrophy is associated with metabolic disturbances, while hyperplasia shows protective activity [2]. Under conditions of positive energy balance, the size and number of adipocytes increases. Increased adipocytes secrete some hormones and cytokines that affect both pre-adipocyte recruitment and pre-adipocyte differentiation into adipocytes. For a chronic positive energy balance, adipocytes become lipid-overloaded and reach a critical size, which leads to inhibition of cellular multiplication and an imbalance between the processes of hypertrophy and hyperplasia [3].

The hypertrophic adipocytes secrete pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), interleukin 8 (IL-8), and monocyte chemoattractant protein 1 (MCP-1) which, through the phosphorylation of insulin receptor substrate-1 (IRS-1), cause insulin resistance. The secretion of these cytokines also recruits macrophages and T-cells, which fuel inflammatory processes. Enlarged adipocytes also cause local tissue hypoxia, which results in the release of hypoxia-inducible factor (HIF-α), leading to inflammation and fibrosis of the AT. If the capacity of the adipocytes is exceeded, lipids start to accumulate in the ectopic tissues, which deteriorates the functioning of these organs and/or tissues [3].

Adipose tissue (AT) is characterized by the presence of various immune cells such as type 2 T-helper cells (Th2), regulatory T-lymphocytes (Treg), eosinophils and type 2 macrophages (M2 macrophages). Treg causes the secretion of anti-inflammatory interleukin 10 (IL-10) and promotes the formation of M2 macrophages which suppress inflammation through the secretion of IL-10. Eosinophils are also characterized by the secretion of anti-inflammatory cytokines interleukin 4 (IL-4) and interleukin 13 (IL-13). This composition of immune cells allows for homeostasis and anti-inflammatory effects [4]. Obesity causes disturbances in the composition of the immune system cells in AT. Hypertrophic adipocytes cause monocytes to migrate to AT and transform them into type 1 macrophages (M1 macrophages). The number of B lymphocytes also increases, which enhances the formation of M1 macrophages. A decrease in the number of eosinophils causes a fall in the secretion of anti-inflammatory cytokines—IL-4 and IL-13. In addition, obesity diminishes the amount of Treg in AT, which results in an increase in cytotoxic $CD4^+$Th1 and $CD8^+$Tc [4][5].

An increased amount of WAT, through increased release of pro-inflammatory cytokines, reduces brown adipose tissue (BAT) activity by inhibiting the induction of uncoupling protein 1 (UCP1). It is associated with a decreased energy expenditure and might be another reason for difficulties in losing and maintaining weight, and obesity [1][6].

2. Adipokines and Their Influence on Pathogenesis, Nutritional Disorders, and Cardiovascular Risk in Chronic Kidney Disease

2.1. Leptin

Leptin is a plasma protein encoded by the obesity gene (ob) that was first described in 1994. It is an anorexigenic hormone that increases energy expenditure. In obesity, increased concentration of leptin occurs, simultaneously with leptin resistance [7]. Reduced leptin activity on the hypothalamus impairs appetite suppression [8].

Enlarged adipocytes are characterized by increased secretion of leptin. Thus, adipokine, by binding to leptin receptors in the central nervous system, causes increased activity of the sympathetic nervous system, which, consequently, can lead to obesity-related hypertension [9]. Hypertension is inextricably linked with kidney failure. Although hypertension is one of the greatest risk factors for the development of chronic kidney disease (CKD), it is also a result of impaired renal function. This is manifested by the fact that with the progression of CKD, the incidence of hypertension increases [10].

Leptin increases the expression of the transforming growth factor-β 1 (TGF-β1) gene and other fibrotic factors, such as collagen IV and fibronectin, which stimulate the proliferation of mesangial cells in the kidneys [11]. Excessive production of these cells can lead to glomerulosclerosis through mesangial hypertrophy in the glomeruli, thickening of the glomerular basement membrane, and increased extracellular matrix [12]. In turn, glomerulosclerosis, by increasing the permeability of the glomerular barrier, contributes to proteinuria and impaired renal function [13].

Leptin-induced vascular endothelial dysfunction is another mechanism that links altered adipokine secretion in obesity with impaired renal function. Leptin stimulates the formation of reactive oxygen species (ROS) that impair the vascular response to acetylcholine, thereby initiating reduced bioavailability of nitric oxide and oxidative stress [14]. In addition, leptin modulates the immune system response. The hormone increases the number of T-helper cells and reduces the number of Treg. It also increases the phagocytic activity of macrophages and increases the TNF-α, IL-6, and interleukin 12 (IL-12). For hyperleptinemia, the balance of pro- and anti-inflammatory processes is disturbed and inflammation occurs [15].

In CKD, metabolic degradation in the renal tubules and glomerular filtration is disturbed, which leads to an increase in the concentration of leptin in the blood. The concentration of leptin increases with the progression of the disease [12][16][17]. Korczyńska et al. observed increased expression of leptin in subcutaneous adipose tissue (SAT) among 5th stage CKD pre-dialysis and dialyzed patients [18]. In stages 3–5 of CKD, without dialysis, altered adipokines profile and insulin resistance were associated with VAT, SAT, and intrahepatic fat [19]. Leptin levels are higher in hemodialysis (HD) women than HD men [20].

Leptin influences nutritional status and CVR among the mentioned group of patients. Patients with CKD are at risk of developing protein-energy wasting (PEW), which is associated with a high risk of mortality. The prevalence of PEW among dialyzed patients is up to 80% [21]. One of the mechanisms influencing their occurrence is leptin concentration disturbances. Leptin has catabolic properties such as increasing the metabolic rate and inducing anorexia [22][23]. The secretion of neuropeptides and neurotransmitters involved in the regulation of appetite occurs as a result of Janus Kinase-2 (JAK2) activation caused by the association of leptin with its receptors (ObRb). Leptin increases the secretion of α-melanocyte-stimulating hormone (α-MSH) and cocaine- and amphetamine-regulated transcript (CART), stimulating feeling of satiety, inhibits the synthesis of secretion of one of the strongest appetite stimulants, for example, neuropeptide Y (NPY) [24][25][26]. The concentration of serum NPY increases, but cerebrospinal fluid (CSF) NPY decreases with the progression of CKD. A low concentration of CSF NPY was associated with cachexia, reduced energy intake, and muscle-wasting among CKD patients [27]. It has been observed that higher serum NPY levels prognosticate cardiovascular mortality among dialysis patients [28][29].

It has also shown that high levels of leptin among CKD patients are associated with inadequate energy and protein intake, and also with reduced levels of muscle mass [30]. Markaki et al. observed that higher leptin levels in HD and peritoneal dialysis patients were associated with greater fat mass index (FMI) and female gender [31]. On the other hand, other was suggested that patients with PEW have lower leptin levels, which could be related to decreased fat mass. Leptin levels are positively correlated with inflammatory markers, which also affects the risk of malnutrition development [32][33]. More are needed to understand the mechanism by which leptin affects the occurrence of PEW.

It has been observed that higher serum NPY levels prognosticate cardiovascular mortality among dialysis patients. Leptin contributes to CVD by causing oxidative stress, inflammation, and endothelial cell proliferation [34]. This adipokine increases platelet aggregation and affects the concentration of vascular endothelial growth factor (VEGF), which leads to

angiogenesis. Vascular endothelial dysfunction contributes to the development of atherosclerosis, which is the basis of many cardiovascular diseases [17][35]. Furthermore, leptin promotes cardiac hypertrophy by mitogen-activated protein kinase (MAPK) signaling [36].

Lu et al. observed that higher serum leptin levels among patients with CKD were a risk factor of aortic stiffness, measured as the carotid–femoral pulse wave velocity (cfPWV). It was conducted among 205 patients with CKD stage 3–5 without dialysis and kidney transplantation (KT). Other risk factors of aortic stiffness were higher systolic blood pressure (SBP) and older age [37]. Similar results were obtained in HD patients and those after KT. In addition, for Kuo et al., elevated serum leptin level among HD patients was correlated with body mass index (BMI) and fat mass [38][39]. It was found that leptin levels were associated with CVR among HD patients only with a larger waist circumference (>102 cm) [40].

2.2. Adiponectin

Adiponectin, a 244 amino acid protein, plays an important role in insulin sensitivity by increasing fatty-acid oxidation and reducing gluconeogenesis. Adiponectin has two types of receptors—adipoR1 and adipoR2 [41][42]. The former is found in all tissues and the latter mainly in the liver. The adipoR1 receptors in the excretory system are present in the proximal tubule cells and the glomerulus cells, for example, in the cells of the endothelium, podocytes, mesangium, and the epithelium of Bowman's capsule. Adiponectin crosses the glomerular filtration barrier, binds to the adipoR1 receptor on the above-mentioned structures and acts on them by activating the adenosine monophosphate-activated protein kinase (AMPK) pathways [42]. AMPK stimulation induces ATP formation processes, including fatty acid oxidation, which protects against obesity and metabolic disorders, and thus indirectly protects the proper functioning of the kidneys. However, in obesity, the concentration of adiponectin is reduced. Kidneys are exposed to the harmful effects of increased levels of pro-inflammatory adipokines and are devoid of the protective effects of adiponectin. Adiponectin may also play a role in the development of obesity-related albuminuria [42][43][44].

The reduced concentration of adiponectin causes translocation of the zonula occludens (ZO-1) proteins from the podocyte epithelial layer into the cytosol. The ZO-1 proteins are structural tight-junction proteins that are responsible for the tightness of the epithelium and the proper function of slit diaphragms. The slit diaphragm is the structure found between the foot processes of the podocytes and acts as a sieve to prevent high-molecular-weight proteins from entering the urine. The structural proteins of slit diaphragms are nephrin and podocin, which determine the proper functioning of this structure. Additionally, low levels of adiponectin have been associated with low levels of nephrin in the renal cortex, which increases the permeability of the filtration barrier [45]. Adiponectin has opposite actions to leptin. Contrary to the action of leptin, decreased levels of adiponectin result in increased synthesis of TGF-β1. This results in cell hypertrophy and increased collagen synthesis, which causes renal fibrosis [46].

Adiponectin has a protective effect on the vascular endothelium. It inhibits the action of the endothelial transcription factor —nuclear factor-kappa β (NF-κβ), through the activation of AMPK. The reduction in NF-κβ activity in the endothelium inhibits the expression of pro-inflammatory adhesion proteins such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1). It causes the adhesion of monocytes to the endothelium of blood vessels, which is a key point in the development of atherosclerosis. On the one hand, this directly affects the renal structures. If the damage to the blood vessels occurs within the kidneys, it leads to a reduction in blood flow and local ischemia of the cells. It causes cell death or damage to their structure and kidney damage. On the other hand, the ongoing inflammatory process further increases renal dysfunction [47].

In addition, the low concentration of adiponectin leads to increased activation of NADPH oxidase 4 (Nox4) and the formation of oxidative stress [48]. Excessive amounts of ROS produced by mitochondria can lead to cellular damage and the progression of renal dysfunction [49].

Adiponectin levels are reduced in obesity, atherosclerosis, and metabolic syndrome. Despite the frequent occurrence of metabolic disorders, patients with CKD treated conservatively have from two to three times higher concentrations of serum adiponectin compared to healthy people. In patients requiring dialysis, the concentrations are even higher [50][51]. After successful KT, adiponectin levels decrease [52].

Adiponectin affects the nutritional status and CVR of patients with CKD. Increased serum adiponectin level is associated with lower BMI, waist circumference, albumin level, female sex, and older age [53][54][55]. Inverse associations were also observed among adiponectin levels and SAT, VAT, total body fat, and lean body mass [56]. Moreover, it was suggested a negative correlation between adiponectin levels and hand-grip [57]. Adiponectin may also affect bone turnover. It has been observed in HD patients that higher levels of adiponectin correlate with a decline in bone mineral density [58]. A high concentration of adiponectin may reflect malnutrition, which indicates a poor prognosis. Hyun et al. assessed the

nutritional status and adiponectin concentration in 1303 pre-dialysis patients. Based on regression analysis, higher adiponectin levels were associated with PEW independent of many other factors [59]. In another, it was conducted among dialysis patients, a positive correlation between adiponectin and Malnutrition Inflammation Score (MIS) was observed, which indicates worsened nutritional status [60][61].

2.3. Zinc-α2-Glycoprotein

Zinc-α2-glycoprotein (ZAG) is a protein secreted by various organs, including AT and renal tubular cells, and is another adipokine that is reduced in obesity. Increased expression of the ZAG gene in AT is caused by glucocorticosteroids and androgens [62]. ZAG regulates the secretion of other adipokines in AT. It reduces the secretion of leptin and increases the secretion of adiponectin. Thus, its low concentration contributes to the persistence of obesity [63]. At physiological concentrations, ZAG increases the expression of peroxisome proliferator-activated receptor γ (PPARγ) and early B-cell factor 2 (EBCF-2) genes by stimulating cyclic AMP (cAMP). This, in turn, initiates an increase in the synthesis of UCP1 and PR/SET domain 16 (Prdm16) proteins, which are involved in the browning process of WAT, which results in increased energy expenditure and leads to lipolysis [64].

ZAG is excreted in the urine due to damage to the basal glomerulus membrane, which may be caused by various glomerulopathies. In diabetic patients, urinary excretion of ZAG increases. It has been suggested that it may be a biomarker of diabetic nephropathy. There is a positive correlation between serum ZAG levels and the value of creatinine and eGFR. Urinary ZAG concentration correlates with the albumin/creatinine ratio [65][66].

Chronic inflammation and elevated leptin levels, which are common in obesity, reduce the secretion of ZAG in AT. Increasing the activity of ZAG in the event of an excessive energy balance may bring health benefits. A negative correlation was observed between ZAG and BMI and the body fat mass in obese subjects [67]. However, in states of catabolism such as cancer cachexia, this adipokine is associated with a deterioration in nutritional status [64].

Patients with CKD have significantly increased plasma levels of ZAG and increased synthesis in WAT compared to the healthy population, which may be associated with impaired renal excretion and the occurrence of uremia [68][69]. Moreover, inflammation and oxidative stress may increase ZAG secretion [70].

ZAG can be a new biomarker of malnutrition due to its lipolytic properties. It activates hormone-dependent lipase (HSL) via cAMP and stimulation of adenylate cyclase [71]. Overexpression of ZAG inhibits lipogenesis by reducing the expression of the genes of enzymes involved in this process, such as fatty-acid synthase (FAS) and acetyl-CoA carboxylase [72]. The serum concentration of ZAG is positively correlated with the serum levels of TG and negatively with HDL cholesterol and albumin levels [73][74].

Obese HD patients have a significantly lower concentration of this adipokine compared with patients with normal body weight [75]. It has been revealed that a negative correlation between the ZAG concentration and the percentage of body fat mass and the sum of skinfolds [76].

Bouchara et al. assessed the effect of ZAG on mortality in HD patients. High ZAG level is a predictor of all-cause mortality and CVR independent of age, or nutritional or metabolic status [71]. In another one, ZAG was negatively associated with TNF-α and VCAM-1, which is a marker of atherosclerosis [76].

2.4. Adipose Triglyceride Lipase

Adipose triglyceride lipase (ATGL) is an enzyme encoded by the patatin-like phospholipase domain containing 2 (PNPLA2) gene. It catalyzes the first lipolysis reaction, for example, the hydrolysis of triacylglyceride (TAG) to diacylglyceride (DAG). ATGL levels are lower in overweight and obese people than in healthy people with normal body weight [77]. Chronic ATGL adipokine deficiency increases the infiltration of immune cells into AT and enhances the inflammatory processes [78]. In terms of kidney function, ATGL deficiency leads to lipid accumulation, damage to the glomerular filtration barrier, and proteinuria. Decreased ATGL levels may increase intracellular ROS formation, which may result in F-actin fiber redistribution, foot-process fusion, and podocyte apoptosis [79]. ATGL gene expression is induced by ZAG in VAT and SAT [80].

As far as it is known, comparison of ATGL concentration in people with normal kidney function and CKD has not been conducted.

Alipoor et al. assessed the concentration of adipokines and nutritional status in HD patients and found that serum ATGL levels were significantly higher in moderate-wasting than in normal-to-mild wasting patients. The increase in ATGL levels

was associated with a 21% increase in the severity of wasting. In addition, ATGL concentration was correlated with TG. ATGL levels are positively correlated with FFAs, which indicates that it affects lipolysis [81]. In another one, ATGL levels did not differ between people with normal and excessive body weight, although there was a direct relationship between ATGL levels and the percentage of body fat mass [75].

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