FUNCTIONS OF ADIPOCYTOKINES AND LINK WITH PRIMARY GLOMERULONEPHRITIS

Beliancinova Monika[1], Blichova Timea[1,2], Kleinova Patricia[1,2], Vnucak Matej[1,2], Granak Karol[1,2], Dedinska Ivana[1,2]

[1]Transplant-Nephrology Department, University Hospital Martin, Slovakia
[2]Clinic of Internal Medicine I., University Hospital Martin and Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovakia

Abstract

Adipocytokines are substances with endocrine functions produced by adipose tissue, playing crucial roles in regulating metabolic functions and inflammatory processes. Dysregulation of fatty tissue's endocrine functions and dysregulation of the production of adipocytokines such as adiponectin, leptin, fibroblast-stimulating factor, and others can lead to a low-grade systemic inflammation and an insulin resistance in patients. These conditions contribute to the pathophysiology of type 2 diabetes mellitus, atherosclerosis, arterial hypertension, metabolic syndrome, and other disorders. Conversely, these metabolic disorders exert feedback-regulatory effects on adipocytokines and their functions.

Glomerulonephritis encompasses a group of immune-mediated diseases characterized by inflammation of the glomeruli. Diagnosis can involve examining urine sediment, detecting autoantibodies, and identifying immune complexes in the blood. However, a kidney biopsy is required for definitive confirmation of glomerulonephritis and is considered the gold standard and a necessity in diagnosis.

Affecting the level of adipocytokines could be one of the new strategies for the pharmacological treatment of many diseases. Given a better understanding of their functions and molecular targets, adipocytokines may herald the emergence of new diagnostic approaches (1, 2). Monitoring the level of adipocytokines could contribute to a better patient management and thus become an auxiliary tool for predicting and diagnosing diseases.

Keywords: adiponectin, leptin, adipocytokines, glomerulonephritis

Abbreviations:

AC	Adipocytokines
ACEi	Inhibitors of angiotensin converting enzyme
anti-GBM	Antibodies against glomerular basal membrane
APN	Adiponectin
BMP-4	Bone morphogenetic protein 4
BMP-7	Bone morphogenetic protein 7
CKD	Chronic kidney disease
CNS	Central nervous system
DM2	Diabetes mellitus type 2
ELISA	Immunoanalytical method
ESRD	End-stage kidney disease
FGF21	Fibroblast growth factor 21
FSGS	Focal segmental glomerulosclerosis
GN	Glomerulonephritis

Corresponding author: Timea Blichová, MD; e-mail: timea.blichova@gmail.com

HLA-DQA1	Major histocompatibility complex, class 2, allele DQ Alpha 1
Ig-dA1	Galaktose-1 deficient IgA1
LN	Leptin
MCD	Minimal change disease
MPGN	Membranoproliferative glomerulonephritis
NPHS1	Nephrin coding gene
NPHS2	Podocin coding gene
PLA2R	Phospholipase A2 receptor
RA	Rheumatoid arthritis
RBP4	Retinol binding protein 4
SGLT2i	Sodium-glucose cotransporter two inhibitor

INTRODUCTION

Adipocytokines are molecules of different sizes produced by adipose tissue and thanks to their endocrine functions they play a role in the regulatory processes of carbohydrate and lipid metabolism in immunological and inflammatory processes. Such substances include leptin, adiponectin, fibroblast growth-stimulating factor, and others. Dysregulation of the endocrine functions of adipose tissue induces the emergence of a low-grade systemic inflammation and an insulin resistance in patients, which can trigger a cascade of pathophysiological pathways with the development of diabetes mellitus type 2 (DM2), atherosclerosis, arterial hypertension and metabolic syndrome, and many others, on the other hand, the aforementioned metabolic disorders have a feedback-regulatory effect on adipocytokines and their functions (3). Glomerulonephritis (GN) is a group of immune-mediated diseases characterized by an inflammation affecting the glomerulus. They are among the diseases that can be diagnosed by examining urine sediment, the presence of autoantibodies, and immune complexes in the blood. They can be unequivocally confirmed only by a kidney biopsy, which is why this examination in diagnosing GN is now considered a necessity and the gold standard. They are divided according to many criteria. The most basic division is the division into primary and secondary glomerulonephritis, and the division, according to the time course of the disease, is into acute, subacute, and chronic. It is also possible to divide them according to the accompanying syndrome (nephrotic/ nephritic/ asymptomatic urinary findings), etiology, and histological findings (different cellularity, morphology, and pathogenesis microscopically and immunohistochemically) (4, 5). In most primary GNs, the etiology is unclear; they are genetically determined, or the trigger is unclear. The overall incidence of GN has decreased in recent decades due to the prevention and therapy of infections in developed countries, but it is increasing in developing countries. An increase in the incidence of GN can occur in connection with antigen exposure due to dietary habits, allergens, and industrial substances (6). In addition to geographic and genetic influences, socioeconomic factors may play a role in developing biopsy findings in some countries. Worldwide, the prevalence of focal segmental glomerulosclerosis continues to increase due to the increasing number of patients with obesity and polypharmacy (7).

The treatment of patients diagnosed with primary glomerulonephritis depends on the biopsy findings and the degree of presentation of the disease in the patient. Affecting the level of adipocytokines could be one of the new strategies for the pharmacological treatment of many diseases, and assuming a better understanding of their functions and molecular targets, adipocytokines may herald the emergence of new diagnostic approaches (1, 2). The aforementioned primary glomerulonephritis and autoimmune disorders also belong to the diseases that adipocytokines can affect. Monitoring the level of adipocytokines could contribute to a better patient management and become a helpful tool for predicting and diagnosing diseases.

GLOMERULONEPHRITIS

Glomerulonephritis is a group of inflammatory diseases of the kidneys, which often arise from unknown causes (primary glomerulonephritis) or are caused by other diseases (secondary glomerulonephritis). It is a group of serious diseases that affect a large number of the younger part of the population and, if left untreated, can lead to rapid progression and kidney failure or chronic kidney disease and the many complications that result from it. In addition to being divided into primary and secondary according to the involvement of other organs, they are divided according to the accompanying syndrome (nephritic or nephrotic syndrome), histological findings in the biopsy sample, and cellularity of the glomeruli, pathogenesis, and duration of the disease (9).

Primary glomerulonephritis

The pathogenesis of primary glomerulonephritis is still not fully understood and is associated with genetic mutations, atherosclerosis, infections or exposure to toxins, and autoimmune processes. Despite detailed investigation of the causes of primary GN, the cause sometimes remains unclear, which is why it is also called idiopathic glomerulonephritis. The origin of some GN lies in the genetic mutation of nephrin or podocin (NPHS1 and NPHS2), complement factor, or other causes. Individual GN names are based on microscopic findings (9).

Immunoglobulin A nephropathy

IgA nephropathy is the most common primary glomerulonephritis (GN). It is accompanied by episodic hematuria and is considered an immune-mediated GN with deposition of insufficiently galactosylated, dimeric, or polymeric immunoglobulin A (IgA) in the glomerular mesangium. Hematuria often occurs alone as a part of or after a respiratory infection. The development of a mesangioproliferative type of glomerulonephritis usually follows this. It mainly affects younger groups of patients, and familial forms of IgA nephropathy occur in Italy. In a low percentage of cases, it has a rapid course, resulting in acute kidney failure (8). There are several views on the optimal therapy of the disease. It focuses on conservative treatment and the use of angiotensin-converting enzyme inhibitors (ACEi) in patients with proteinuria and deteriorating renal function. When using steroids or immunosuppressants, there are different, even conflicting, results. However, new preparations, such as SGLT2 inhibitors (sodium-glucose cotransporter inhibitors), have contributed to a more effective therapy in recent years. Budesonide, which plays a role in regulating the formation of galactose-1 deficient IgA1 (Ig-dA1), which causes IgA nephropathy by depositing Igd-A1, comes to the fore after the successful third phase of testing. (9).

Membranous glomerulonephritis

Membranous glomerulonephritis primarily affects middle-aged and elderly adult patients. In the case of a secondary cause, it can also follow some infections (e.g., hepatitis B and C), cancer, systemic immune diseases (lupus erythematosus), or some medications (e.g., those containing gold or penicillamine) (10). It accounts for about 25% of cases of patients with nephrotic syndrome, about 70–80% of cases of primary membranous glomerulonephritis in Caucasians, represents an autoimmune response against the M-type phospholipase A2 receptor (PLA2R), which can be detected on glomerular podocytes and subepithelial immune foci and glomerular basement membrane it can be thickened due to subepithelial deposits. Polymorphisms of the PLA2R gene in combination with polymorphisms of the human leukocyte antigen DQ-A1 (Major Histocompatibility Complex, Class II, DQ Alpha 1 - HLA-DQA1) increased the risk of developing primary membranous glomerulonephritis up to 79 times (11). The therapeutic procedures are dominated by ACEi and the recommendation of reasonable blood pressure control, corticoids, rituximab, and cyclophosphamide (12).

Membranoproliferative glomerulonephritis

This disease is also referred to as mesangiocapillary GN because, according to the biopsy findings, it is characterized by a thickening of the glomerular basement membrane with mesangioproliferative changes and the deposition of immunocomplexes. MPGN patients show low serum levels of complement C3. It usually occurs in children and adolescents and is rare in African Americans, accounting for approximately 10% of cases of nephrotic syndrome in adolescents (12). Deposits of immunocomplexes in the area of mesangial cells and the glomerular basement membrane cause inflammation, resulting in its proliferation and bifurcation of the basement membrane (GBM). Depending on which part of the GBM the deposits are located, this type of GN is divided into subendothelial MPGN, subepithelial MPGN, and intramembranous MPGN. Secondary MPGN is often associated with neoplasia, hepatitis C, and autoimmune diseases such as lupus erythematosus or cryoglobulinemia. Clinical findings include hematuria, proteinuria, and pyuria, while systemic symptoms such as weakness and fatigue mainly occur in children. In a quarter of cases, there is a picture of rapidly progressing GN and nephritic syndrome together with a rapid decline in renal function. Up to 50% of patients reach the end stage of chronic kidney disease within ten years – kidney failure and up to 90% of patients after 20 years, while nephrotic syndrome, hypertension, and renal insufficiency are predictors of a poor prognosis (9). Corticosteroids and immunosuppressants are used in therapy.

Minimal change disease

This type of glomerulopathy occurs in up to 70–90% of biopsy findings in children but only in approximately 25% of findings in children and 10–15% of findings in adult patients with nephrotic syndrome. It occurs in an idiopathic form or connection with the use of nonsteroidal anti-inflammatory drugs or lithium or as part of a paraneoplastic syndrome. In the microscopic finding (light microscopy), no changes may be present (hence the name), but electron microscopy may show an enhancement of podocyte protrusions and their fusion. Minimal change disease (MCD) is characterized by isolated hematuria. In this case, MCD tends to have a mild course, while ESRD occurs in patients with a significant proteinuria. ACEi and corticosteroids are used in therapeutic approaches. In case of relapses, immunosuppressants are used (cyclophosphamide, calcineurin inhibitors) (12).

Focal segmental glomerulosclerosis

The most common type of GN tends to affect different areas of the glomeruli (segments) but does not entirely affect all (focal). The secondary form usually appears as a reaction to certain drugs (lithium) or diseases (human immunodeficiency virus infection, lymphoma) or as a result of heroin abuse. The incidence of focal segmental glomerulonephritis (FSGS) is increasing in developed countries and is most often manifested by proteinuria. In the clinical picture, it is possible to see severe proteinuria and a rapid decline in renal functions, accompanied by hematuria and hypertension. In the case of FSGS and kidney transplantation, it often appears as a relapse in the transplanted kidney. ACEi, steroids, and cyclosporine are used in therapy, and in case of relapse, rituximab (13).

ADIPOCYTOKINES

Adipocytokines are cytokines, growth factors, complement factors, and other substances of a peptide nature that are produced in adipose tissue. In addition to adipocytes, adipose tissue contains different types of cells with endocrine activity. Precursor and endothelial cells, fibroblasts, foam cells, and macrophages also show secretory activity. They produce bioactive lipids, metabolites, and bioactive peptides – adipocytokines (AC). Adipocytokines are adipose tissue-specific substances of a hormonal nature, such as adiponectin and leptin, vaspin, apelin, visfatin, nesfatin, cathepsins, omentin, fibroblast growth-stimulating

factor 21 (FGF21), retinol-binding protein 4 (RBP4), bone morphogenetic protein 4 and 7 (BMP-4, BMP-7), proteins of the fibrinolytic system, proteins of complement and complement-like proteins, enzymes, lipid transporters, proteins of the renin-angiotensin system, cannabinoids and other lipids and proteins and adipose tissue-specific molecules that are secreted. Still, adipose tissue is not the only place of their formation. The total number of bioactive peptides produced by adipose tissue is thought to exceed 600 different types of proteins (Figure 1).

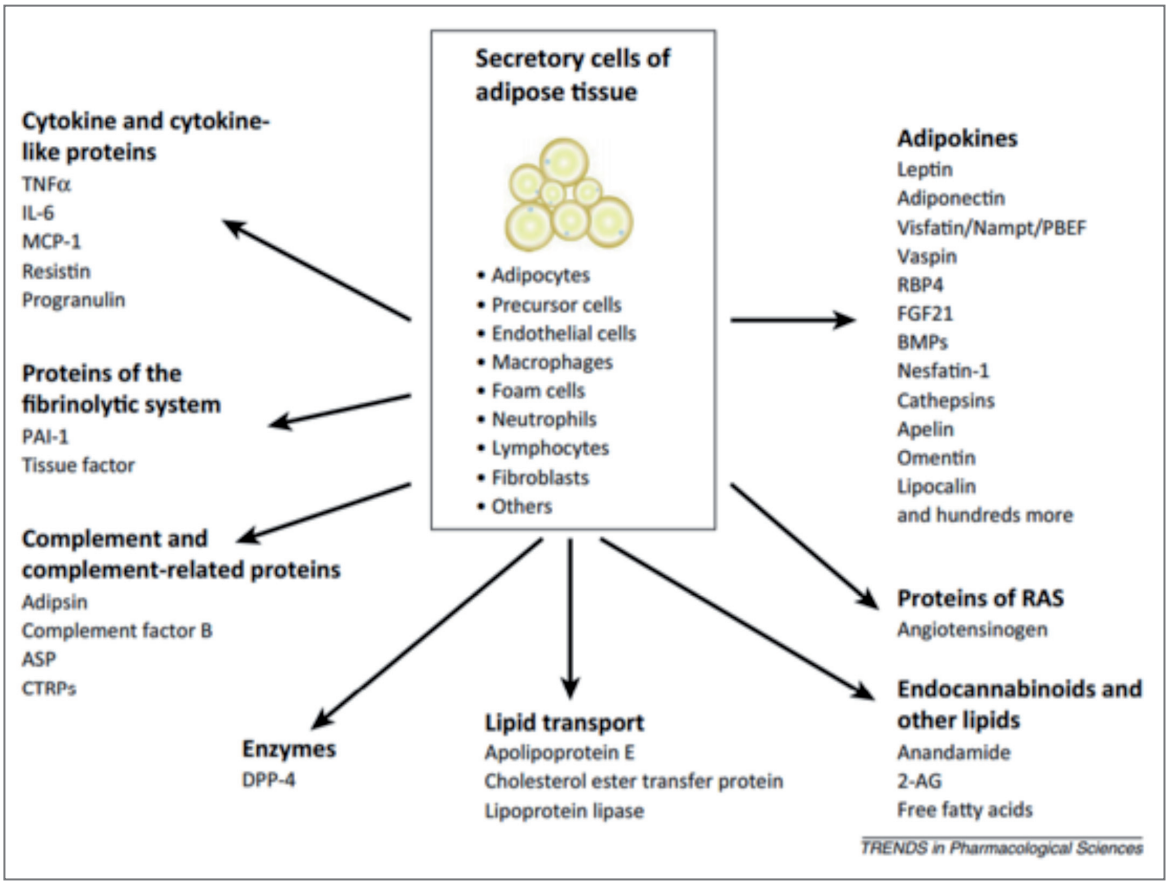

Fig. 1 Factors released or produced by adipose tissue. Adipocytes, immune cells, fibroblasts, endothelial cells and others. Abbreviations: 2-AG, 2-Arachidonoylglycerol; ASP, acylation stimulating protein; BMPs, bone morphogenetic proteins; CTRPs, C1q/TNF-associated factors; FGF21, fibroblasts growth factor 21; MCP-1, a chemotactic protein for monocytes -1; PAI-1, plasminogen activator inhibitor -1; RAS, renin-angiotensin system; RBP4, retinol binding protein 4.
From: FASSHAUER, M., BLÜHER, M.

Dysfunction of the synthesis of these proteins is associated with a spectrum of diseases Dysfunction of the synthesis of these proteins is associated with a spectrum of diseases arising mainly in connection with obesity. Still, adipocytokines mediate information for target organs and structures in all groups of people (1, 14). The accumulation of visceral adipose tissue is the cause of dysregulation of the production of these hormones, which further results in accelerated atherosclerosis and metabolic and cardiovascular diseases.

Adipose tissue was considered only as a storehouse of energy in the form of triacylglycerols, and the molecular basis of these processes still needed to be fully elucidated. Still, many pathophysiological pathways have been discovered in which adipocytokines play key roles (15). One of the main functions of adipocytokines is maintaining glucose homeostasis in metabolism, and obesity (and hypertrophy of adipocytes) can result in their dysregulation and the development of atherosclerosis, a proinflammatory state, and a diabetogenic effect with the development of hypertension, liver steatosis, pulmonary diseases, oncological diseases, and dementia (18, 19).

Patients with hypertrophic adipocytes show higher levels of pro-inflammatory factors, interleukin 6 and 8, leptin and MCP-1, and lower levels of adiponectin and anti-inflammatory interleukin 10 (20, 21).

The overall impact of the secretion of a small adipose tissue area may be negligible, but the total volume of adipose tissue is inter-personally variable. Therefore, AC production may have a multisystemic impact. It is also worth mentioning the rich vascularization of adipose tissue, which facilitates systemic circulation (23).

The most frequently preferred technique for determining the level of adipocytokines in plasma, serum, and cerebrospinal fluid is the immunoanalytical method (ELISA); another method is the Luminex multiplex method based on microparticle analysis. Adiponectin has several multimeric forms: trimers, hexamers, and high molecular weight structure formation in various structural complexes. Adiponectin and leptin exhibit circadian or ultradian rhythms, which must be considered in studies investigating their functions (19). Adipocytokine levels respond to changes in serum insulin levels. It has yet to fully understand what changes in insulin secretion occur with a long-term shift in adiponectin secretion (19–21).

Adiponectin increases tissue sensitivity to insulin, and leptin reduces serum concentrations of triacylglycerols in patients with lipodystrophy, signalling the state of energy reserves in the body to the central nervous system (CNS). It is a polypeptide composed of 244 amino acids, and its receptors, AdipoR1 and AdipoR2, are found in most organs. AdipoR1 is a receptor found primarily in skeletal muscle and AdipoR2 in the liver. The adiponectin concentration in human serum reaches 0.5–30 μg/l. It is located on chromosome 3q27, which is a site associated with susceptibility to developing diabetes mellitus and is associated with various diseases in which inflammation plays a role, for example, in the development of cardiovascular disease, metabolic syndrome, rheumatoid arthritis, and osteoarthritis, probably due to its action on the innate and adaptive immune system (24–27). Some studies identify APN as a new marker of MS onset. This assumption is based on the negative correlation of MS with APN levels (28). Hypoadiponectinemia can be considered a predictor of myocardial infarction or the development of hypertension (29–31). Arthritis and MS patients have lower APN levels than arthritis patients who do not have MS. In RA patients, low adiponectin levels were hypothesized to be involved in the development of cardiovascular disease and RA. Still, in RA patients treated with antiTNFα, adiponectin concentrations were independently and inversely correlated with high levels of inflammation (32).

The occurrence of proteinuria is associated with the nephrotic syndrome present in many cases of patients with primary glomerulonephritis, such as primary glomerulonephritis such as FSGS, membranous glomerulonephritis, IgA nephropathy, minimal change disease, but the proinflammatory contribution of some adiponectin isoforms cannot be associated with all cell types in the body. The question is, therefore, whether the pro-inflammatory effect that occurs in patients with these diseases also has a reverse effect for further deterioration of glomerular filtration or whether this pro-inflammatory condition applies more in other tissues than in the kidneys (11, 12). Increased adiponectin concentrations in plasma can have different effects, and it is still not completely clear which isoforms are most involved in its protective effect.

Table 1 The most frequently described adipocytokines with some of their effects and roles in metabolism. From Blüher et al., 2013 and HILL et al., 2009

Adiponectin	Antidiabetic, antiatherogenic, anti-inflammatory
Leptin	Regulation of satiety, appetite, food intake, activity and energy expenditure, fertility, atherogenesis, growth induction
Apelin	Inhibition of insulin secretion
Vaspin	A serine protease inhibitor reduces food intake, increases hyperglycemia, and insulin-sensitizing effects.
Progranulin	Chemoattractant, neurodegenerative diseases, inflammation of adipose tissue
Chemerin	Chemoattractant, regulation of adipogenesis
TNF-α	Proinflammatory, high correlation to BMI
IL-6	Proinflammatory expression increases with age and adiposity, reducing CRP expression in the liver.
PAI-1	Inhibition of plasminogen activators, atherogenesis
FABP-4	Associated with an increased risk of developing DM2, myocardial contractility
RBP4	Associated with the development of insulin resistance, the distribution of visceral fat
Nesfatín-1	Direct insulinotropic glucose-dependent effect on β-cells
Visfatín/PBEF/Nampt	Nampt-mediated systemic NAD biosynthesis is critical for β-cell function.
MCP-1	Chemoattractant, adipose tissue inflammation
Fetuin-A	Fat-induced inflammatory reactions, insulin resistance, progression of oncological processes
Omentin	Anti-inflammatory increases insulin sensitivity
DPP-4	Degradation of GIP and GLP-1 inhibitors in clinical trials for DM2
Clusterin	Promotion of progression of oncological processes and angiogenesis
Acylation stimulating protein	Anabolic effect – affects the degree of synthesis of triacylglycerols in adipose tissue.
Transforming growth factor β	Increased secretion is related to increasing BMI and inhibition of adipocyte differentiation.
Adrenomedullin	Wide range of action: effective vasodilator, inhibits insulin secretion, anti-apoptotic effect

Leptin is a 16-kDa protein consisting of 167 amino acids free or bound to proteins in the body. Its circulating amount is directly proportional to the amount of fat, and its level typically ranges between 0.5 15 ng/ml in humans, mice, and rats. This is why mouse models are so often used in research. Leptin signalling depends on the leptin receptor found on target cells. It plays crucial roles in regulating satiety, appetite, food intake, reproductive functions, fertility, puberty, activity and energy expenditure, atherogenesis, intrauterine development, and modulating immune reactions. In the hypothalamus, leptin can reduce the proportion of orexigenic and increase the proportion of anorexigenic genes, which results in a change in the individual's appetite in the sense of a decrease in appetite (25, 33, 34).

Some studies have shown a correlation between adiponectin and leptin and eGFR, proteinuria, and other laboratory and objective parameters in patients with identified primary glomerulonephritis. They found a positive correlation of leptin with BMI and the level of triacylglycerols but did not confirm the correlation with proteinuria (35). The authors of the British study experimented with wild-type mice and obese leptin-deficient mice (ob/ob) and administered nephrotoxic globulin. In ob/ob mice, they found the absence of glomerular thrombosis and the formation of crescentic structures in the glomeruli. They performed three experiments to rule out the influence of the higher weight of ob/ob mice with a dose adjustment of nephrotoxin. In comparison, in all three experiments, ob/ob mice did not show a histological kidney damage and also showed a significantly lower albuminuria and no hypoalbuminemia. According to this experiment, the blockade of the leptin synthesis pathway can be an exciting possibility that influences autoimmune diseases, including glomerulonephritis (36). The following table provides an overview of the effects of individual adipocytokines.

CONCLUSION

Affecting the level of adipocytokines could be one of the new strategies for the pharmacological treatment of many diseases. Moreover, assuming a better understanding of their functions and molecular targets, adipocytokines may herald the emergence of new diagnostic approaches. Monitoring the level of adipocytokines could contribute to a better patient management and become a helpful tool for predicting and diagnosing diseases.

However, it is necessary to remember that the detection of AC as biomarkers and their quantitative measurement is still limited nowadays because commonly known diseases and their pathomechanisms, including obesity, insulin resistance, and visceral adipose tissue accumulation, are easily diagnosed. A complete diagnosis of these diseases does not require detecting markers such as true adipocytokines or oncological or immune-related diseases.

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