An Overview About Adiponectin and Correlation with Hypertension

Mohammed Ghanem Gabr [1], Amir Mohamed Elokely[2], Mabrouk Ibrahim Ismail [2], Nafesa Mohammed Kamal [2], Samia Hassan El-Shishtawy [1]

1 Internal Medicine and Nephrology Department, Faculty of Medicine, Zagazig University, Egypt

2 Internal Medicine and Nephrology Department, Theodor Bilharz Research Institute

Corresponding author: Mohammed Ghanem Gabr

E-mail: Ghanemnephrologist@gmail.com

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Abstract

Adiponectin is a 244-amino-acid protein that is mostly produced by adipose tissue. It serves as an anti-inflammatory, insulin-sensitizing, and vasculoprotective cytokine. Adiponectin has been extensively investigated in relation to lipoprotein metabolism, whose dysregulation is known as dyslipidemia. Increased triglycerides, free fatty acids, and low-density lipoprotein (LDL) and a reduction in high-density lipoprotein (HDL) are frequently indicators of obesity. Endometrial dysfunction, hypertension, myocardial infarction, and other complications of metabolic syndrome, as well as the onset and progression of cancer, may all be primarily caused by obesity-related deregulated adiponectin production. The sympathetic nervous system's activation, endothelial dysfunction (caused by an increase in free fatty acids and oxidative stress), and aberrant adipokine synthesis are a few of the mechanisms that contribute to the link between obesity and hypertension. Adiponectin levels are decreased in adults with hypertension. In comparison to lean and normotensive people, it was discovered that obese people with hypertension had lower levels of total adiponectin. Blood pressure is coordinated by adiponectin using endothelium and brain-controlled pathways. We are witnessing a continuous rise in the prevalence of obesity and hypertension. Both disorders are predominant risk factors for cardiovascular disease, and the latter is the leading cause of morbidity and mortality worldwide. Obesity may induce hypertension through multiple mechanisms, including endothelial dysfunction, RAS hyperactivation, SNS overdrive, and renal-pressure natriuresis impairment.

Keywords: Adiponectin, Hypertension

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Introduction

Adiponectin is a 244-amino-acid protein that is mostly produced by adipose tissue. It serves as an anti-inflammatory, insulin-sensitizing, and vasculoprotective cytokine *(1)*.

Sources of adiponectin

Adiponectin was assumed to be produced exclusively by adipose tissue at first. but it was found that adiponectin is expressed in several tissues, including human osteoblasts, liver parenchyma cells, myocytes, epithelial cells, and placental tissue. The circulating concentration of adiponectin is high, constituting 0.01% to 0.05% of total plasma proteins *(2)*.

Structure of adiponectin

The Adipo Q gene**,** which spans 17 kb on chromosome 3q27, encodes human adiponectin. The start codon for human adiponectin is located in exon 2, whereas the end codon is located in exon 3. The area of human chromosome 3q27 that contains a susceptibility gene for T2DM, and metabolic syndrome has been found *(3)*.

Recent studies demonstrated the validity of urinary adiponectin as a marker of the progression of focal segmental glomerulosclerosis, albuminuria, incident cardiovascular disease, and renal function deterioration, as well as diabetic nephropathy. More recently, some research groups have also noticed the relationship between adiponectin levels and diabetic nephropathy *(4)*.

Adiponectin receptors

AdipoR1 and AdipoR2 are two types of adiponectin receptors that have been discovered**.** There are seven transmembrane domains in both receptors. In vivo, the primary receptors for adiponectin are AdipoR1 and AdipoR2, with AdipoR1 activating the adenosine 5′-monophosphate–activated protein kinase (AMPK) pathways and AdipoR2 activating the peroxisome proliferator-activated receptor (PPAR) pathways. Endothelial cells, podocytes, mesangial cells, and Bowman capsule epithelial cells are the four cell types that make up the glomerulus, and they all express the adiponectin receptor AdipoR1. It's also seen in kidney proximal tubular cells. Because of the receptor's position, it's possible that adiponectin and its receptors have an impact on renal physiology and pathology in obesity and diabetes *(5)*.

AdipoR1 is primarily expressed in muscles, whereas AdipoR2 is primarily expressed in hepatocytes. Both types of receptors are found in practically every tissue, however one type usually predominates in a given tissue. Furthermore, the degree of affinity of these receptors for various types of adiponectin differs. AdipoR1 has a strong affinity for globular adiponectin (a cleaved version of full-length adiponectin), but a weak affinity for full-length adiponectin, whereas AdipoR2 is in the middle. Both receptor types are upregulated by hypoadiponectinemia, which is linked to IR. Physical activity causes overexpression of the adiponectin hormone system, implying a link between exercise-induced insulin resistance improvement and the adiponectin hormone system *(6)*.

Downstream signaling events of adiponectin

Adiponectin triggers a cascade of signaling processes in the body. APPL1 (Adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1) is an adapter protein that binds to adiponectin receptors and positively modulates adiponectin signaling interacts directly with insulin receptor substrates and operates as a signaling pathway mediator in crosstalk with adiponectin and insulin. The p85 regulatory component of the phosphatidylinositol 3-kinase (PI3K) uses insulin receptor substrate proteins as docking platforms, resulting in the formation of phosphatidylinositol 3,4,5-triphosphate at the plasma membrane. The PI3K pathway is activated, which activates it and its downstream targets, resulting in a physiologic response. The AMP activated protein kinase (AMPK) is triggered by APPL1. APPL1 binds and activates protein phosphatase 2A in response to adiponectin binding to its receptor, causing protein kinase Cz (PKCz) to be dephosphorylated and inactivated. This allows liver kinase B1 (LKB1) to translocate from the nucleus to the cytoplasm and activate AMPK ***(7)***. AMPK activation is a crucial step in mediating most of adiponectin's cellular actions. AMPK is a fuel-sensing enzyme that responds to cellular energy depletion by activating energy-generating pathways (e.g., fat oxidation) and inhibiting energy-consuming pathways; nevertheless, AMPK is not required for survival (e.g., fatty acid, triglyceride, and protein synthesis). Adiponectin raises the expression and activity of PPAR-α, a major transcription factor in metabolic control, which promotes fatty acid oxidation and energy expenditure by upregulating acetyl CoA oxidase (ACO) and uncoupling proteins (UCPs). Adiponectin's impact on p38 MAPK and Ras-related protein 5 *(*Rab5), a Glutamyl Transpeptidase *(*GTPase) downstream of APPL1, increases glucose metabolism in a variety of metabolic organs. Activated AMPK is also implicated in nitric oxide synthesis through the activation of eNOS, which results in vasodilation, in response to adiponectin. Furthermore, adiponectin activated AMPK suppresses apoptosis mediated by IKK/NFB/PTEN ***(6)***.

Obese State and Adiponectin

As opposed to other known adipokines, adiponectin has a negative correlation with both central adiposity and body mass index (BMI); the strongest negative correlation has been seen with the waist-to-hip ratio. It is without a doubt regulated at the transcriptional, translational, or post-translational levels by a feedback loop. Its receptors AdipoR1 and AdipoR2 have similarly shown a similar tendency of downregulation. Following weight/fat loss, normal levels of adiponectin and its receptors are restored. Although several mechanisms have been put forth, none of them fully explain the feedback mechanism in the regulation of adiponectin ***(8)***.

The inflammatory cytokines IL6, IL8, TNF-α, and leptin, which are directly known to suppress adiponectin transcription, are significantly elevated in an obese state, which is a condition of chronic inflammation in the body. The most significant and well-known function of adiponectin is the insulin sensitization of skeletal muscles. While glucose signaling in response to food intake stimulates elevated insulin secretion by the pancreas, which is free from adiponectin's regulatory

control due to its lower circulating concentrations, an increase in visceral fat mass lowers systemic adiponectin levels, causing insulin resistance in the skeletal muscle ***(8)***.

Adiponectin has been extensively investigated in relation to lipoprotein metabolism, whose dysregulation is known as dyslipidemia. Increased triglycerides, free fatty acids, and low-density lipoprotein (LDL) and a reduction in high-density lipoprotein (HDL) are frequently indicators of obesity.

Adiponectin and Hypertension

Endometrial dysfunction, hypertension, myocardial infarction, and other complications of metabolic syndrome, as well as the onset and progression of cancer, may all be primarily caused by obesity-related deregulated adiponectin production ***(9)***.

The sympathetic nervous system's activation, endothelial dysfunction (caused by an increase in free fatty acids and oxidative stress), and aberrant adipokine synthesis are a few of the mechanisms that contribute to the link between obesity and hypertension. Adiponectin levels are decreased in adults with hypertension. In comparison to lean and normotensive people, it was discovered that obese people with hypertension had lower levels of total adiponectin. Blood pressure is coordinated by adiponectin using endothelium and brain-controlled pathways ***(10)***.

Adiponectin lowers TNF-α and prevents macrophages from transforming into foam cells, according to studies. Nitric oxide (NO) generation via the phosphoinositide 3-kinase (PI3K) and AMPK pathways in endothelial cells is inhibited by adiponectin, preventing the development of atheroma. Additionally, TNF-α and smooth muscle cell proliferation and macrophages are decreased by adiponectin ***(8)***.

Atherosclerosis

Numerous mechanisms connect cardiovascular diseases and obesity. The "adipo-cardiovascular axis" is a crosstalk between adipose tissue, the heart, and arteries that is facilitated by a number of adipokines. The altered release of adipokines promotes a prothrombotic condition that results in atherosclerosis and cardiovascular disease. Serum adiponectin levels below normal serve as indicators of atherosclerosis and myocardial infarction ***(10)***. Additionally, there is a strong link between hypoadiponectinemia and coronary heart disease that is well supported by clinical studies, which also show that lower levels of adiponectin are linked to a higher incidence of cardiovascular events. According to research, HMW adiponectin is a more effective independent risk factor for heart disease than total adiponectin ***(8)***.

Adiponectin in hypertensive nephropathy

The increasing relevance of adiponectin in kidney disease has been demonstrated in numerous studies. Heart disease (CVD) continues to be the leading cause of morbidity in this group of people. Malnutrition, atherosclerosis, ongoing inflammation, and increased oxidative stress are

additional risks. Likewise, hypoadiponectinemia and microalbuminuria have been linked in clinical studies to patients with hypertension. Patients with ESRD have two to three times greater serum adiponectin levels than people with good renal function, despite having a poor metabolic condition. Adiponectin secretion from adipose tissue has risen, which contributes to this in part *(11)*.Patients on either peritoneal dialysis or hemodialysis have serum adiponectin levels that are roughly three times greater than those of the normal population, and neither treatment significantly reduces adiponectin. According to research, oxidative stress, and sympathetic nervous system activity, which are frequent in chronic renal disease, are factors that cause reduced adiponectin secretion *(12)*. They all assert that adiponectin action in CKD patients may be blocked, despite the fact that these results are partially contradictory *(11)*.

Omentin-1

Omentin is an adipokine whose gene is produced mostly in stromal vascular fraction cells of adipose tissue. It is also known as intelectin, intestinal lactoferrin receptor, endothelin lectin HL-1, and galactofuranose-binding lectin *(13)*.

Structure

Omentin is a novel adipokine of 313 amino acids. Visceral adipose tissue produces it more frequently than subcutaneous adipose tissue.

There are two isoforms of it: omentin-1 and omentin-2. The primary type of omentin found in human blood is omentin-1 *(14)*.

The omentin gene is found on chromosome 1q21.3, which has been linked to type 2 diabetes. The development of inflammatory disorders is influenced by this adipokine. It improves cardiovascular health, glucose metabolism, energy homeostasis, and the decrease of oxidative stress. Omentin-1 also exhibits protection against atherosclerosis, cancer, and metabolic bone disease *(15)*.

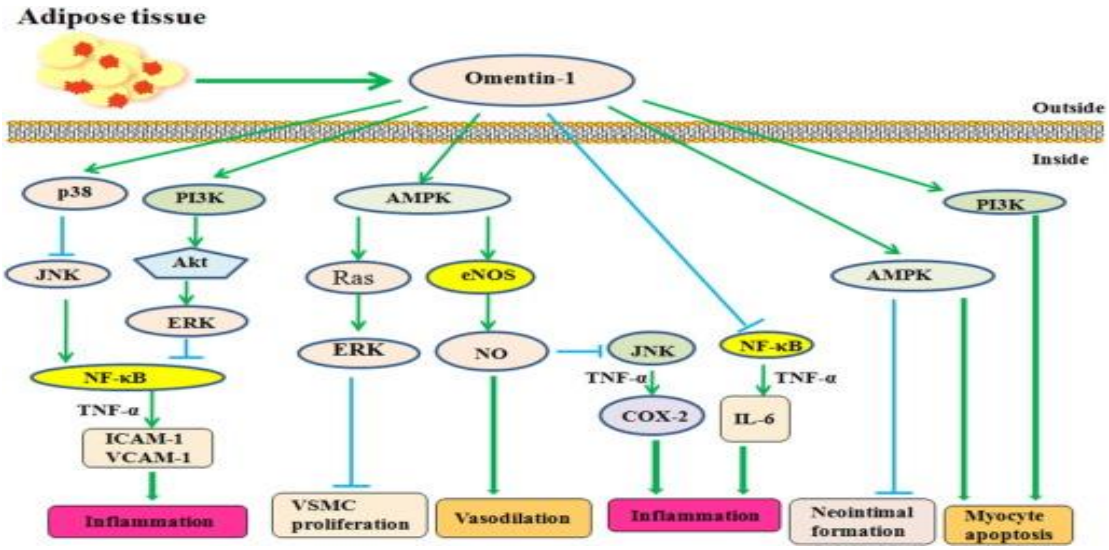

Figure (1): Omentin signaling pathway, TGF-β, transforming growth factor-β; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; PI3K, phosphatidylinositol 3- kinase; AKT, protein kinase B; AMPK, AMP-activated protein kinase; TNF-α, tumor necrosis factor-α; JNK, c-Jun N-terminal kinase; VSMC, vascular smooth muscle cell; COX-2, cyclooxygenase-2; PDGF-BB, platelet-derived growth factor-BB; NO, nitric oxide *(16)*.

Omentin and obesity

Omentin may play a significant role in the prevention of metabolic conditions linked to central obesity. Reduced omentin levels are linked to a higher risk of type 2 diabetes and other health issues related to being overweight *(17)*.

Numerous investigations into the correlation between omentin concentrations and anthropometric measurements have produced contradictory findings. Omentin concentrations have been reported to rise following a low-calorie diet, while reduction diets have been proven to lower this adipokine's levels *(18)*.

According to studies, lean female participants and women with extreme obesity had considerably different levels of omentin gene expression in visceral adipose tissue. Additionally, it was discovered that obese women had significantly lower serum omentin concentrations than women of normal weight. Another study, however, evaluated omentin levels across patients with and without obesity and discovered no statistically significant variations between the two groups. Omentin levels in the serum of women with and without obesity were compared, and no differences were found. The female gender physiologically has a higher percentage of adipose tissue than the male gender, which is also important to note. Serum omentin concentrations and body weight, BMI, and fat mass content [%] all exhibited negative relationships. Among obese women, the first two correlations were particularly significant *(19)*.

Omentin and hypertension

Studies revealed that Omentin-1 has anti-atherosclerotic, anti-inflammatory, and cardiovascular protective actions in addition to playing significant roles in insulin sensitivity and body metabolism. Omentin-1 was found to cause vasodilation via raising endothelial nitric oxide synthase and lowering TNF-α in in vitro tests. The association between these pro-inflammatory cytokines and the physiopathology of hypertension could assist in explaining why those suffering from hypertension have low Omentin-1 levels.

Omentin-1 level was shown in patients with non-alcoholic fatty liver to have a negative connection with systolic blood pressure when compared to normotensive controls. It was observed that serum Omentin-1 levels were lower in hypertension patients. The combined effects of endothelial dysfunction, renal damage, and inflammation in the presence of hypertension may be responsible for these lower levels *(20)*.

Furthermore, Cinemre et al. *(21)*, reported that omentin levels I their study population tended to increase according to the grade of hypertension, although their results were not significant statistically.

Omentin 1 and hypertensive nephropathy

The adipokine omentin has significant antioxidative and anti-apoptotic effects, but more importantly, it may slow the course of atherosclerosis by encouraging normal vasculature remodeling *(7)*. Omentin-1 levels have been found to be altered in ESRD patients receiving chronic hemodialysis, where it has predictive value for the development of vascular disease and cardiovascular mortality. However, the link between this adipokine and subclinical atherosclerosis in the context of ESRD is still unclear *(22)*.

A recent study showed that renal patients with severe disease may have Omentin-1 involved in the development of atherosclerosis *(22)*.

Interlukin-6

Interlukin-6 (IL-6) is a multifunctional cytokine that has both pro- and anti-inflammatory effects in humans. Generally, it goes under a variety of names depending on its biological sources and roles. Because it was cloned to isolate and characterize the virally induced protein interferon-β, it was given the name interferon-β2 *(23)*.

It has now been referred to as the 26 K factor, B-cell stimulatory factor 2, hybridoma growth factor, plasmacytoma growth factor, hepatocyte stimulatory factor, hematopoietic factor, and cytotoxic T-cell differentiation factor *(24)*.

Normal values range from 1 to 5 pg/ml, although they are raised in conditions like cancer, infection, and autoimmune diseases *(25)*.

Structure

A single chain phosphorylated glycoprotein called IL-6 mostly consists of four helix bundles (A–D). The ribbon-like representation of the helices A and B, which run in one direction while C and D run in the other. The second short chain between helices C and D that is not part of the primary four-helix bundle (A-D) is known as helix E. IL-6 sends its signals via a cell-surface type I receptor complex made up of the gp130 signaling subunit and the ligand-binding glycoprotein known as the IL-6 receptor (IL-6R). The 80 kDa -chain IL-6R is also known as CD126 *(24)*.

IL-6 interacts by means of the trans-signaling pathway, sIL-6R, or the classical signaling pathway, mIL-6R. In both instances, IL-6 binds to the receptor first and subsequently, via CBD domains, to gp130, but depending on the receptor type, produces various physiologic effects *(26)*.

Leukocytes and liver cells, which express both mIL-6R and gp130, are the key sites where classic signaling is seen. This enhances the anti-inflammatory responses. Trans-signaling, on the other hand, can be seen in any cells that express gp130 and promotes pro-inflammatory reactions *(23)*.

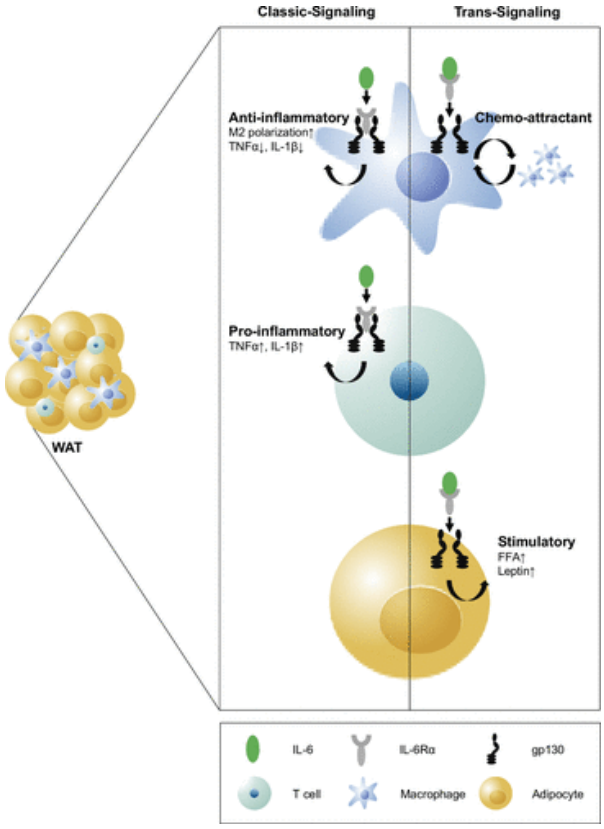

Figure (2): Classical IL-6 receptor signaling and IL-6 trans-signaling pathways *(26)*.

IL-6 and obesity

A state of chronic inflammation occurs in obese people as a result of the excess of macronutrients in adipose tissues, which triggers the release of inflammatory adipokines like IL-6, TNF- α, monocyte chemoattractant protein-1 (MCP-1), and resistin *(27)*.

Regarding immune cell composition and quantity, the WAT of obese persons differs from that of lean individuals. It has been demonstrated that different innate and adaptive immune cell types invade the obese WAT. Macrophages are a significant component of invading innate immune cells, and depending on their polarization, they can perform a variety of activities in WAT. Two kinds of polarized macrophages—M1 proinflammatory and M2 anti-inflammatory macrophages—were established *(28)*.

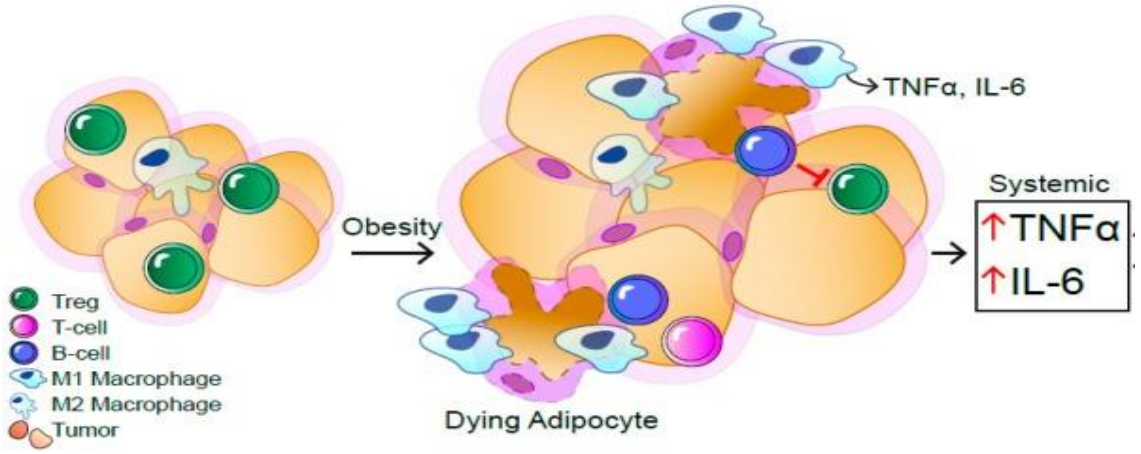

Figure (3): The obesity-induced, systemic, low-grade *(28)*.

Obese patients, as well as those with chronic inflammatory diseases and anomalies in blood lipid concentrations, were shown to have higher serum levels of IL-6. Increased levels of IL-6 in obese people may lead to an increase in type 2 diabetes risk, insulin resistance, and cardiovascular complications. It was determined that IL-6 is released into the circulation in an adequate concentration to cause endocrine effects by measuring the arteriovenous difference of IL-6 over the abdominal subcutaneous adipose tissue under basal conditions. It was discovered that adipose tissue releases one-third of the total amounts of circulating IL-6 *(26)*.

Body mass index and plasma IL-6 levels have been shown to positively correlate in postmenopausal women. The strong positive connection between blood levels of IL6 and BMI in healthy subjects with obesity was one of the study's key findings, according to Baikpour et al. *(29)*.

Additionally, it was discovered that a high level of circulating IL-6 may indicate the severity of the systemic and chronic inflammation that results from extreme obesity, which may both directly and indirectly promote the development of atherosclerosis and coronary heart disease *(30)*.

Il-6 and hypertension

One of the most significant cardiovascular risk factors is hypertension. Evidence suggests that even in prehypertensive patients, complex immune responses, including elevated inflammatory mediators, are implicated in the inflammatory process of hypertension. Chronic inflammation may be the cause of the increased vascular permeability, thrombogenesis, and fibrosis that are side effects of persistent hypertension. Chronic inflammation causes endothelial dysfunction by causing proinflammatory cytokines to produce more ROS. In hypertension patients, elevated serum levels of proinflammatory cytokines like IL-1 β, IL-6, IL-8, IL-17, IL-23, TGF β, and TNF α have been linked to either elevated blood pressure or end-organ damage *(25)*.

Through its effects on vascular inflammation, stiffness, and endothelial dysfunction, IL-6 may contribute to the pathogenesis of HTN. Additionally, it promotes the production of fibrinogen

and inhibits the breakdown of arterial wall collagen. It's interesting to note that atherosclerotic plaques have higher IL-6 levels. Increased IL-6 and TNF-α serum levels have been hypothesized as separate risk factors for the development of high blood pressure in otherwise healthy people, suggesting that IL-6 may potentially be useful as a biomarker. In patients with hypertension, a relationship was identified between plasma levels of IL-6 and TNF-α with coronary endothelial dysfunction *(31)*.

According to a study by Oluboyo et al. *(32)*, hypertensive disorder individuals had higher levels of IL-1 and IL6. IL-1 and IL-6 can therefore be used to assess and track hypertension cases in order to stop inflammatory complications from developing in hypertensive people.

Furthermore, regardless of blood pressure levels, some cytokines, such as IL-6, appear to determine a hypertensive response to angiotensin II *(25)*.

Il-6 and hypertensive nephropathy

The primary risk factors for CKD include cardiometabolic disease, particularly diabetes but also obesity, hypertension, and CVD *(33)*.

Researchers discovered that IL-6 expression was elevated in the kidneys of patients with CKD and even further elevated in the kidneys of patients with CKD and hypertension, suggesting that IL-6 plays a significant role in angiotensin-II-induced hypertension and CKD *(34)*.

It is widely believed that IL-6 plays a significant role in the development or progression of CKD. This is because of its harmful net effect on the renal cells. As a result, it has been demonstrated that systemic IL-6 levels are high even in early-stage CKD and that they are a reliable predictor of death in later-stage CKD. Elevated IL-6 levels may be a symptom of CKD rather than solely a pathogenic component, according to research that suggests impaired function may also result in a reduced renal clearance of IL-6 *(35)*.

We are witnessing a continuous rise in the prevalence of obesity and hypertension. Both disorders are predominant risk factors for cardiovascular disease, and the latter is the leading cause of morbidity and mortality worldwide. Obesity may induce hypertension through multiple mechanisms, including endothelial dysfunction, RAS hyperactivation, SNS overdrive, and renal-pressure natriuresis impairment

No Conflict of interest.

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