Review Article

The complex effects of adipokines in the patients with kidney disease

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Kidney diseases are categorized as the highest prevalent ones with worldwide noticeable incidence. They cause accelerated cardiovascular diseases and noticeable mortalities. Adipose tissue and its messengers, adipokines, are reported to have the highest relationship with end-stage renal diseases or chronic kidney diseases. Over recent years, with shifting of scientists' mindset from a simple overview of adipose tissue as a fat store to the complex paradigm of this issue as a multipotential secretory organ, the importance of studies on this tissue has emerged.

Key words: Adipokines, adipose tissue, kidney diseases

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INTRODUCTION

Kidney disease is a global health burden with high prevalent as well as high economic cost, of which chronic kidney disease (CKD) is the most famous disorder in the category. It is associated with hypertension, cardiovascular disease (CVD), obesity, and renal dysfunction with five stages, in which stage 3 is the major among the CKD patients. The global prevalence is between 11% and 13%.[1] In the US, the latest report pointed out to 14.8% CKD prevalence with the same, most prevalent stage to the global statement with considerable health cost and medicare.[2] Various factors have been found to have a direct relationship with kidney disease; among them, adipose tissue and adipokines contribute more than other biological elements.[3-5] In recent years, adipokines have become an important part of multipotential secretory organ as well as its role in the biology of a variety of organs in the human body. Understanding the adipobiology of diseases can guide us to get familiar with adipokines that target pharmacology better.[6] There are different adipokines members with various roles in health and diseases.[7] Sometimes, there are controversial ideas about the impact of adipokines in the pathobiology of kidney diseases.[8] Here, the different roles of each important adipokine are discussed.

METHODS

This review was written according to the previous articles with the topic of adipose tissue, adipokines, and their association with Vitamin D. Our keywords were considered as our searching topics and the articles which were published after 2000 were chosen. The literature was collected from PubMed/Medline, EMBASE, Scopus, and Web of Science, and relative information was reviewed meticulously.

ADIPONECTIN AND KIDNEY DISEASE

Adiponectin is a 30-kDa protein from adipose tissue, circulating in the plasma with trimer form.[4,9] Adiponectin is the most available adipose tissue protein which has a suggested anti-atherosclerotic and anti-inflammatory function. The anti-inflammatory feature is due to its effect on vascular walls and suppression the proinflammatory molecules via the

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help of nuclear factor kappa B (NFκB) signaling pathway. It can also inhibit the subsequent proinflammatory effects by suppressing of tumor necrosis factor (TNF)-α and interleukin (IL)-6 and promoting anti-inflammatory cytokines such as IL-10.[10]

Plasma level of adiponectin and intercellular adhesion molecule (ICAM)-1 can predict albuminuria, and the anti-inflammatory property of adiponectin in kidney injury is probably due to the inhibition of ICAM-1. Increasing ICAM-1 triggers immune cells, especially macrophage, to accumulate in the kidney which is associated with fibrosis, albuminuria, and decline of renal function. Adiponectin can decrease the expression of adhesion molecules in the kidney endothelial cells in response to inflammatory stimuli.[11] Similarly, it has been reported that adiponectin is positively correlated with proteinuria and albuminuria and it is inversely related to body mass index (BMI) and renal function.[12] However, there is an opposite finding that lower level of adiponectin can predict the albuminuria.[13] In addition, in the low level or the absence of enough adiponectin, the level of IL-6 and high-sensitive C-reactive protein (hs-CRP), which is responsible for the renal disorder and atherosclerosis, is increased. The reason is raised by the vasculoprotective actions and anti-inflammatory property of adiponectin in comparison with the presence of IL-6 and hs-CRP in inflammatory states such as obesity.[14] Experimental studies demonstrated that overexpression of adiponectin results in improved proteinuria in early diabetic nephropathy (DN) and endothelial dysfunction,[15] and in adiponectin knockout mice, renal fibrosis and albuminuria are increased, considerably.[16] According to the above statement, it seems that adiponectin has a protective role in the kidney diseases by inhibition of microvascular damage,[17] and lower level of adiponectin in the plasma is in association with the progression of kidney disease.[13] Nevertheless, high adiponectin was reported to be the predictor of CKD progression in male patients.[18]

On the other hand, the following controversial reports have stated the relationship between adiponectin level and the risk of cardiovascular diseases. Some reports have revealed that high level of adiponectin is associated with lower cardiovascular risk factors.[19,20] In one study, it has been reported that a lower level of adiponectin in the plasma is in association with the past and new CVD events in patient suffering renal failure.[21] Fatal and nonfatal cardiovascular events have also observed to be inversely correlated with lower plasma adiponectin.[22] Some others have suggested that higher plasma adiponectin level is associated with increased cardiovascular risk factors and further renal dysfunction.[23,24] Rare investigations failed to find any association between plasma adiponectin level and cardiovascular events.[25] However, the controversial reports seem to be due to different inherited and environmental elements.[9]

Furthermore, in nondiabetic end-stage renal disease (ESRD) patients, the mRNA expression of adiponectin is upregulated in the subcutaneous and visceral fat tissue. This overexpression was not observed in diabetic patients.[26] The possible explanation for this difference between two above groups may be because of the association of a low level of adiponectin and diabetes mellitus.[18] In both mentioned groups, the expression of adiponectin receptor type 1 (AdipoR1) is increased in the peripheral blood mononuclear cells (PBMCs) and various tissues.[26,27] Another important adiponectin receptor, AdipoR2, is also overexpressed only in PBMCs.[26,27]

The above statements about the role of adiponectin showed that low-circulating adiponectin is a strong risk factor for CVDs, albuminuria, and also hypertension. Furthermore, in CKD patients, the higher level of adiponectin has been reported to have an adverse correlation with progression of CKD.[9] However, opposite ideas[8] seem to remain an unsolved question about the exact role of adiponectin in the kidney progression.

LEPTIN AND KIDNEY DISEASES

Leptin is secreted by adipocytes and demonstrates the body fat. In CKD disease, obesity and hypertension have a central role in renal injury and vascular dysfunction. Leptin is reported to be increased considerably in patients with CKD.[8] In an animal model study of spontaneously hypertensive which is received the high-fat diet, the level of cholesterin and leptin is increased.[28] Moreover, a higher level of leptin and cholesterol leads to vascular dysfunction via upregulated reactive oxygen species (ROS) and nitric oxide (NO) metabolites.[29] The endothelial dysfunction is related to renal injuries and further higher cardiovascular risk.[8]

ESRD patients have a higher level of leptin compared with healthy control.[30] It has been reported that serum leptin concentration is increased in CKD patients which is correlated to the level of CRP. The above-mentioned finding demonstrated the connection between hyperleptinemia and inflammation with CKD pathogenesis.[31] The following findings report that urinary leptin level is lower in these patients due to not degradation of leptin, which remains high in the glomerular filtration rate (GFR).[32] On the other hand, a short-term use of leptin showed no effect on urinary protein excretion. In a long-term treatment with leptin, the animal study demonstrated that urinary protein excretion is increased.[33]

With the increased size of adipocyte, the secretion of leptin is increased, which is positively correlated with BMI.[16] Kidney produces a receptor for leptin named *ob*-Ra. This isoform is not complete and cannot bind to leptin well. Besides, kidneys can produce a lower complete isoform of leptin receptor called *ob*-Rb. Due to leptin being bound to *ob*-Ra, which is expressed on mesangial and glomerular endothelial cells, and the exceed leptin not being absorbed, it can stimulate a variety of different cellular system mechanisms such as stimulating of transforming growth factor-beta (TGF-β) 1, type IV collagen, as well as phosphatidylinositol-3-kinase (PI3K), leading to producing some proinflammatory cytokines and other mediates, which participates in the renal failure and kidney dysfunction.[8] The results of other investigations prove the claim because an increased TGF-β has been observed in renal tubular and mesangial cells in the leptin-treating group, which has an important role in leptin-induced nephropathy.[34]

VISFATIN AND KIDNEY DISEASES

Visfatin is predominantly secreted by adipose tissue and enriched in the visceral adipose tissue. It influences the energetic metabolism by participating in the nicotinamide adenine dinucleotide synthesis. An interesting finding of this protein is that it can induce production of both anti-inflammatory and proinflammatory cytokines.[35] The level of circulating visfatin is increased dramatically in CKD patients and is associated with renal function and soluble vascular cell adhesion molecule (VCAM)-1, as a key marker of endothelial damage.[8] In patients, as well as in an animal model of type 2 DN, the level of visfatin is increased. Therefore, visfatin is seemed to be as a proinflammatory adipokine in metabolic syndrome and type 2 diabetes.[8] The other investigations have indicated that administration of visfatin induces secretion of proinflammatory and profibrotic molecules such as type 1 collagen, plasminogen activator inhibitor 1, and TGF-β.[36,37]

Yilmaz *et al*. found that circulating level of visfatin was associated with endothelial dysfunction.[38] Mu *et al*. reported that higher level of visfatin is associated with endothelial dysfunction, atherosclerosis, and lipid dysregulation in patients contracted with CKD.[39] Axelsson *et al*. stated that renal function influences circulating level of visfatin; however, they could not find any significant association between markers of insulin resistance with visfatin level in CKD patients.[40] Carrero *et al*. reported that in CKD patients with poor appetite, visfatin is increased and has an adverse correlation with triglyceride (TG) and fasting serum amino acids.[41] Mahmood *et al*. found that except for significant positive association between level of visfatin and CKD, there was no difference for visfatin concentration in diabetes and nondiabetes CKD patients. Furthermore, negative correlation with GFR and positive correlation with proteinuria were reported.[42]

RESISTIN AND KIDNEY DISEASE

In 2001, resistin was discovered, and soon after that, it was revealed that it has an association with endothelial damage, inflammation, and insulin resistance.[43] The main source of resistin is visceral adipose tissue-resident macrophage. It has been reported that resistin contributes to the increased risk of atherosclerosis, CVDs, and insulin resistance diseases. Its serum concentration is increased in the CKD and type 2 diabetes patients.[8] Independent association of resistin and GFR in the early stage of hypertension expresses the involvement of this protein in the kidney damage progression. Resistin promotes the expression of adhesion molecules, endothelin, and matrix metalloproteinases and stimulates systemic vascular dysfunction which affects GFR.[44] Furthermore, positive correlation of leukocyte counts, endothelin-1, and CRP with resistin has been revealed.[45]

In the CKD patients, the serum level of resistin is negatively associated with GFR.[46] Likewise, Marouga *et al*. reported that an increased level of resistin is associated with a decline in the GFR and may participate in the malnutrition–inflammation state. In addition, they found that TNF-α and hs-CRP were the most important independent determinants of serum resistin level.[47] Resistin can induce expression of adhesion molecules such as ICAM-1 and VCAM-1. This induction can be inhibited by adiponectin, ICAM-1, and VCAM-1 through a negative feedback mechanism, as well as other inflammatory markers such as IL-6 and CRP, which is positively correlated with resistin in the patients with CKD.[46] Furthermore, this correlation is seen in patients with renal transplant and animal model with diet-induced obesity.[48]

The molecular experiment has shown that resistin through the NFκB pathway can carry out its effect on the overexpression of inflammatory molecules, including IL-6 and TNF-α.[49] In the ESKD, resistin is reported to increase significantly, which was weakly correlated with inflammation and was not associated with insulin sensitivity and was negatively correlated with adiponectin level. Interestingly, the relationship between resistin level and all-cause death and cardiovascular events depended on adiponectin levels that mean adiponectin can modulate the inflammatory effect caused by resistin and other inflammatory elements.[50]

OMENTIN AND KIDNEY DISEASE

Omentin is a 313 amino acid protein which is mainly expressed in the visceral adipose tissue, which has a link

with type 2 diabetes.[51] Except for adipocytes, stromal vascular cells can also produce omentin.[51] There are two kinds of omentin: type 1 and type 2. Omentin-1 is predominantly released in the visceral adipose tissue; however, omentin-2 is abundantly expressed in the intestine.[52] Clinical investigations have demonstrated that administration of metformin in patients with polycystic ovary syndrome increases the serum level of omentin-1 and change in the omentin is negatively associated with hs-CRP.[53] Omentin increases uptake of insulin-induced glucose through activated Akt cellular pathways.[51] The level of omentin is positively correlated with adiponectin.[52] The study on human microvascular endothelial cells cultured with normal serum showed that omentin suppresses NFκB activity, TNF-α, and CRP.[53] The cell culture of human umbilical vein endothelial cells showed that omentin can decrease apoptotic activity and enhance blood flow recovery and differentiation into the vascular-like structure and also capillary density in the ischemic limb of mice.[54]

In the ESRD patients receiving hemodialysis, the plasma level of omentin has been reported to be about 1.7 times higher than that of healthy people.[55] On the other hand, in the CKD patients, the serum level of omentin was reported lower compared with healthy subjects. What's more, it has been reported that in the diabetic CKD patients, the level of omentin is lower than that one in nondiabetic patients. Furthermore, compared to healthy controls, omentin level was lower in stage 2 and 3, but not in stage 4, and an overall decrease in the omentin has been linked with increased inflammation and malnutrition components.[56] In another study conducted on nondiabetic, not dialyzed CKD patients, the serum level of omentin-1 was higher in the patient group compared with healthy population. However, they were failed to find an association between omentin-1 and marker of inflammation (IL-6).[57] In the study into the patients with kidney disorders, the serum level of omentin-1 was significantly lower in the diabetic hemodialysis ones compared with nondiabetic hemodialysis patients. Their hypothesis was based on decrease in omentin-1 linked to atherosclerosis through an effect on the vascular endothelial in inflammatory condition.[58]

Moreover, circulating omentin is introduced as a novel biomarker of endothelial dysfunction. Circulating omentin is correlated with CRP, IL-6, BMI, fat mass percentage, blood pressure (both systolic and diastolic parameters), and independent vasodilation in the normal glucose tolerance subjects and is correlated with systolic blood pressure, BMI, insulin sensitivity, and CRP in the impaired glucose tolerance people.[59] In hemodialysis patients, omentin-1 is introduced as the potential biomarker of subclinical atherosclerosis.[60] In insulin resistance CKD patients, plasma level of omentin-1 was higher compared to healthy controls and was associated with insulin resistance in hemodialysis patients.[61] Nevertheless, the report in the hemodialysis diabetic patients was completely inverse.[62] According to a recent study, the detection of serum omentin level, which was lower in patients with microalbuminuria than in nonmicroalbuminuria and healthy control, can play a pivotal role in early diagnosis and prevention of DN in patients with type 2 diabetes mellitus.[63]

Omentin seems to play a pleiotropic role in the regulation of metabolism and maintain body to be healthy; however, all in all, it is categorized as a good adipokine with beneficial effect on longer survival rate in patients with various diseases such as diabetes, insulin resistance, cancer, endothelial dysfunction, and atherosclerosis.[64] In other words, despite not fully understanding of omentin functions, an increase in the level of omentin seems to be a marker for leanness, while the decreased level brings about the situation for overweight and obesity along with their comorbidities.[65]

APELIN AND KIDNEY DISEASE

Apelin is an adipocytokine produced in the white adipose tissue and expressed in the various organs, including endothelium, heart, and kidney.[66] It is a 36 peptide amino acid from a 77 amino acid precursor that, after some modifications in various organs, has several forms including apelin 36, 19, 17, 15, 13, 12, and 10. Apelin has a special receptor called APJ.[67] It has a potential link with obesity and insulin sensitivity,[68] and it is involved in the pathophysiology of cardiovascular disease in chronic renal failure.[69] In these patients, apelin has been reported to be positively associated with E-selectin and VCAM.[69] However, another study indicated that plasma apelin is not associated with cardiovascular risk in hemodialysis patients.[70]

In kidney allograft recipients, apelin was correlated with coronary artery disease (CAD) and diabetes, and ICAM, adiponectin, and CAD were the predictors of apelin in them; it was significantly decreased. Except for CAD, endothelial damage and inflammation were also predictors of the presence of apelin which indicates the presence of apelin in that it and other adipocytokines may have a direct link with inflammation and disease' exacerbation.[71]

Cellular study of apelin in the DN and measurement of its effect to disease exacerbation indicated that serum apelin level was positively correlated with microalbuminuria. In addition, apelin with its receptor participates in the development of DN. A further step of the study suggested that apelin may regulate glucose metabolism in diabetes. Further, the author reported that apelin may be a pivotal

factor for pathological glomerular angiogenesis and facilitates abnormal vessel formation in the diabetic glomeruli, which contributes to the DN development. Apelin induces proliferation of glomerular endothelial cells and has a significant role in the pathological glomerular angiogenesis. Microalbuminuria and overt proteinuria are the common early signs of DN. In this study, the author found that serum apelin was positively correlated with microalbuminuria in type 2 diabetic patients.[72] On the other hand, experiment on the mice with type 1 diabetes reported that apelin retards the progression of DN. It did not affect the blood pressure, glycemia, and body weight, and interestingly short and long treatment with apelin showed that clinical inflammation manifestations were significantly reduced informing that apelin has the protective role in the diabetic kidney.[73] Confirmed reports stated that the level of apelin in the ESRD patients was negatively correlated with hs-CRP and IL-6, and after transplantation for these patients, the mentioned level was significantly increased.[74]

Apelin-13 is one of the most important peptides with paramount biological functions. A study on patients with maintenance hemodialysis without heart failure in the pre- and post-dialysis courses about the association of serum apelin-13 level with asymmetric dimethylarginine (ADMA), as an important factor for the activity of NO synthase (NOS) and production of NO which is contributing to the inflammation, showed that both concentrations were increased and there was a positive correlation which would be affective on the blood pressure.[75] Furthermore, an animal study demonstrated that apelin-13, which regulates the inflammation in DN via regulation of histone acetylation, as an important factor, has a beneficial effect on the treatment approaches.[76] A similar study indicated that apelin-13 may be a therapeutic candidate for treating acute kidney injury (AKI) by inhibiting TGF-β.[77] In agreement with the above-mentioned statements, another study suggested that apelin has potential renoprotective effects and may be an effective agent for retarding CKD progression.[78] In addition, apelin ameliorates vascular calcification by suppressing osteoblastic differentiation of vascular smooth muscle cells via downregulation of sodium-dependent phosphate cotransporter.[79] The complex effects of apelin on the regulation of renal hemodynamics are already determined.[80]

OTHER ADIPOCYTOKINES AND KIDNEY DISEASE

Vaspin

Vaspin or visceral adipose-derived serine proteinase inhibitor is an adipokine identified in the animal model of type 2 diabetes.[81] It is related to obesity and insulin resistance in human. In patients with type 2 diabetes, the clinical investigations indicate that the level of vaspin is higher than that of normal subjects,[82,83] although the similar level in the mentioned groups has also been seen.[84] The clinical evaluation of serum vaspin in hemodialysis patients has revealed the higher concentration compared with healthy subjects.[85] Nonetheless, another result found that mean serum vaspin was not significantly different between hemodialysis patients and healthy population.[86] Furthermore, it has been reported that the serum TG and creatinine of all subjects were independently associated with serum vaspin.[85] Similarly, positive association between vaspin concentrations and serum creatinine was indicted.[86] On the other hand, in type 2 diabetes, microvascular complications were found associated with low vaspin levels. This finding was in parallel with glycemic control by metformin in those patients. It might be due to medications interfering with serum vaspin.[87]

Since vaspin has 50-KDa molecular weight, it cannot be eliminated efficiently in the hemodialysis patients, and furthermore, because other adipokines such as adiponectin or leptin are observed usually higher in ESRD patients, it could be a unique feature in these patients. Moreover, due to the positive correlation of vaspin with BMI and albumin, it could be a representative for nutritional status.[85] An animal study showed that administration of vaspin significantly reduces blood glucose and food intake.[88] Molecular activity evaluation of vaspin shows that it has an inhibitory effect on ADAM as a competitive endothelial NOS (eNOS) inhibitor, which is a potential atherosclerosis risk factor, and therefore, it has an antiatherogenic and antiapoptotic effect on vascular endothelial cells. Due to its important role of vaspin on vascular cells, it acts as a compensatory factor.[89]

Chemerin

Chemerin is a multifunctional protein found throughout the body which has various receptors, including chemokine-like receptor 1 (also known as ChemR23) and C-C chemokine receptor-like 2, and G protein-coupled receptor-1.[90] It is a 16-kDa protein modulating immune responses and affecting lipid and glucose metabolism.[91] Chemerin is one of the most important biomarkers of cardiovascular disease in diabetic CKD patients.[92] In general, it seems that it would be a chemokine to immune cells or an adipokine for adipose tissue. It has a regulatory effect on adipocyte growth and lipid metabolism, and it is predominantly produced in the liver, found in high concentrations in the white adipose tissue.[90] A study on the human showed that chemerin has a positive effect on low-density lipoprotein and has a negative association with high-density lipoprotein cholesterol in obese patients.[93] It has also been stated that chemerin plays a role in the adipogenesis.[94] The mRNA level of chemerin and its receptor was found higher in mature adipocytes. In addition, the intensity of mRNA expression is higher in the high-fat diet condition.[95]

Chemerin has a positive correlation with inflammatory markers, including IL-6, CRP, and TNF-α.[96] In other words, it has proinflammatory functions in various diseases.[97] In an early study on the level of cheremin in the CKD patients, it has been found that mean serum level was about two-fold higher in CKD patients than subjects with GFR >50 ml/min. Moreover, GFR was an independent predictor for circulating cheremin level in both healthy and CKD patients.[98] In type 2 diabetic patients, the level of serum chemerin was found to be higher in macroalbuminuria patients than in microalbuminuria and normoalbuminuria patients. In comparison with healthy people, it has also been found that only macroalbuminuria had a significant difference in terms of serum chemerin level among three above groups. In this study, the authors declared that renal function factors such as creatinine clearance had a significant association with serum chemerin.[99]

In ESRD patients who prepared for transplantation, the level of serum chemerin was evaluated, which was decreased significantly after 3 months of transplantation, compared with the time before the operation. Serum creatinine was also reduced and GFR was improved.[100] Another study confirmed that serum chemerin was normal after renal transplantation. During hemodialysis procedure, the serum level of chemerin remained higher than in healthy subjects or kidney transplantation.[101] The only reasonable explanation for higher chemerin level in patients with kidney diseases[102] is related to renal dysfunction,[101] and according to the studies on genetic expression of chemerin in CKD compared to healthy control, which was not significantly different,[101] as well as its level in the adipose tissue which was not related to overproduction,[101] possible causes of elevated circulating chemerin do not seem to be related to genetic factors, and elevated circulating chemerin levels that depend on renal function are not genetically determined.[103] On the other hand, due to the considerable complications of the high level of chemerin in CKD patients,[104] this issue should be targeted at the next clinical studies.

Progranulin

Progranulin is a cysteine-rich secreted protein with 68–88-kDa molecular weight.[105] It expresses in a variety of cells such as immune cells, epithelial cells, adipocytes, and neurons.[106] It has wound repair and tissue remodeling properties,[107] as well as early embryogenesis and growth factor-like features,[108] which regulates cell division, survival, and migration by regulation of ERK and PI3K signaling pathways.[107] Association of progranulin with the alteration of adipocytes which results in progression to obesity has been survived. It consequently leads to insulin resistance and initiation of type 2 diabetes mellitus.[109]

A clinical study on the kidney showed that progranulin serum level depends on the renal function. In various stages of CKD (1–5), it has been reported that serum progranulin is significantly different, being highest in the ESKD. It has also been found that GFR is an independent predictor factor for circulating serum progranulin. Moreover, it seems that progranulin is involved in the proinflammatory state among patients with renal disease.[110] Therefore, similar to the previous statements of chemerin, renal filtration is the most pivotal efficient factor, eliminating the progranulin. In diabetic kidney disease, progranulin has also been found to have a crucial role in the pathophysiology renal decline and it can be used as an early prognostic factor for diabetic kidney disease.[111] Moreover, it is introduced as a marker for diabetic microangiopathy and its severity.[112] Nevertheless, progranulin plays a protective role with anti-inflammatory properties in the kidney of patients with renal ischemia–reperfusion injury.[113]

Interleukin-1, interleukin-6, tumor necrosis facor-alpha, and C-reactive protein

IL-1 is divided into two important subtypes of IL-1α and IL-1β. Both are involved in the inflammatory responses in different parts of the animal and human bodies. Lots of studies have been carried out to indicate the exact role of IL-1 in the kidney function. In an animal model of AKI, necroinflammation commonly occurs. Mutant mice are protected against renal necroinflammation.[114,115] In CKD models, IL-1 plays an inflammatory role in the exacerbation of CKD. It appears that IL-1 contributes to leukocyte adhesion and vascular leakage, which leads to a systemic endothelial dysfunction. Intrarenal inflammasome, as well as renal parenchymal cell necrosis by IL-1 and other inflammatory factors, results in renal dysfunction.[116]

IL-6 is a pleiotropic cytokine with various functions. In IgA nephropathy, immune complex and complement component stimulate mesangial cells to release IL-6 which causes proliferation and recruitment of inflammatory factors and immune cell, involved in the necrosis of renal cells. In DN, proteinuria is observed due to elevated proinflammatory cytokines such as IL-6.[117,118] Hyperglycemia can trigger tubules, podocytes, mesangial cells, and interstitial tissues, which participate in the systemic inflammatory process in DN.[119,120] Furthermore, both type 1 and type 2 diabetes are positively correlated with increased IL-6 level.[121,122] *In vitro* studies on the IL-6 showed that IL-6 induces insulin resistance.[123,124] IL-6 has also a direct relationship with AKI. Clinical findings demonstrated that IL-6 signaling and transcription are increased in ischemic AKIs.[125] In CKDs, IL-6 is observed to remain high.[126] Meantime, infiltrated IL-6 is due to a reduced clearance and renal dysfunction which contributes to the accumulation of IL-6. This issue

consequently results in inflammatory responses and an increase in the IL-6 production.[127,128]

TNF-α is a proinflammatory cytokine and necessary part of tissue damage. It comes from macrophages infiltrating adipose tissue and kidney.[8] TNF-α, as well as IL-6, mediates chronic and acute inflammation in a variety of disorders such as patients with kidney disease[129] and cardiovascular disease.[130] Limitation of TNF-α in an animal model with renal failure leads to a reduction of renal inflammation and fibrosis.[131] TNF-α is associated with the prevalence and severity of CKD.[132] This relationship is reported in various clinical and epidemiological studies.[133,134] Besides, TNF-α receptor-2 is positively associated with developing risk of CKD.[135] One of the main reasons for this observation comes from a lack of proper clearance in the renal and elevated inflammatory cytokines, leading to progression of renal dysfunction.[136] In addition, in kidney, TNF-α contributes to angiotensin II-dependent hypertension, independent of blood pressure. Deficiency in TNF-α in thw kidney increases renal eNOS expression, resulting in increased bioavailability of NO.[137] With the various roles of TNF-α in the inflammatory kidney diseases,[138] a more precise study with better framework should be done to understand the pathophysiology of TNF-α in kidney disorders.

CRP is an acute-phase reactant. Although it does not belong to adipokines due to its noticeable role in kidney pathogenesis, it provides beneficial information about inflammation status of the disease. It has been reported that CRP is not significantly increased in CKD patients.[132] The confirmed results approve this finding.[134] However, other reports stated that CRP can be a predictor of mortalities in hemodialysis patients.[139] In chronic dialysis patients, CRP is found to be a risk factor of death.[140] Another investigation found that CRP predicts all-cause and CVD mortality in hemodialysis patients.[141] In CKD patients with type 2 diabetes, CRP is positively associated with severity and progression of the disease.[142] Furthermore, CRP is found to have a significant association with eGFR,[133] while others declined any relative association.[132,135,143]

CONCLUSION

Kidney diseases have become one of the fast-growing diseases with many interrelated comorbidities. Recent epidemiological data have proven the necessity of especial global monitoring for both diagnosis and prediction of diseases through the evaluation of above-mentioned factors. Despite emerging strategies and constant investigation, still, we face many problems in the treatment. If we are not able to reverse or at least stop the disease progression, is it time to change our mind and monitor other elements such as adipokine due to their beneficial and detrimental ramifications?

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