The Role of Monocyte Chemoattractant Protein-1 (MCP-1) in Diabetic Kidney Disease

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A B S T R A C T

Monocyte chemoattractant protein-1 plays an important role in kidney disease. In several studies, the role of MCP-1 as a urine biomarker has been extensively studied. In many kidney diseases, there are elevated levels of MCP-1 in the kidney tissue and this is an important cause of monocyte infiltration in the pathogenesis of kidney damage. Elevated urinary MCP-1 levels have been able to predict outcome in proliferative kidney diseases such as lupus nephritis. However, in several studies it was also found that there was an increase in MCP-1 in diabetic kidney disease. Macrophages have even appeared early in diabetic kidney disease and are associated with the progression of kidney disease. Urinary MCP-1 levels are related to the degree of leukocyte infiltration in the tubulointerstitial. This supports inflammatory factors as part of the pathogenesis of diabetic kidney disease.

1. Introduction

Diabetic kidney disease (DKD) is one of the most frequent complications of diabetes mellitus. Renal dysfunction develops in one in three patients with diabetes. Diabetic nephropathy is characterized by albuminuria, glomerulosclerosis, and a progressive decline in kidney function. Therapy for diabetic kidney disease current DKD, which includes blood sugar control, angiotensin II receptor blockers, and ACE inhibitors, appears to slow – but not stop – the process leading to renal failure after diabetic nephropathy is established.[1-3] Monocyte chemoattractant protein-1 (MCP-1) is a chemokine consisting of 76 amino acids measuring 5-20 kDA, which is a potent chemotactic factor for monocytes. Chemokines are among the first chemokines to be discovered in humans and are the most studied to date. These chemokines play a major role in the pathogenesis of various organ system disorders. Monocyte chemoattractant protein-1 is produced by mesangial cells, podocytes, and monocytes in response to various proinflammatory stimuli. These inflammatory cells and their substances, in turn, mediate tissue damage and contribute to renal dysfunction.[4-7]

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the pathogenesis of kidney damage. Elevated urinary MCP-1 levels have been able to predict outcomes in proliferative kidney diseases such as lupus nephritis. However, in several studies, it was also found that there was an increase in MCP-1 in diabetic kidney disease. Macrophages have even appeared early in diabetic kidney disease and are associated with the progression of kidney disease. Urinary MCP-1 levels are related to the degree of leukocyte infiltration in the tubulointerstitial. This supports inflammatory factors as part of the pathogenesis of diabetic kidney disease. In patients with diabetic kidney disease, an increase in MCP-1 in kidney tissue and urine indicates that macrophages play a role in the development of kidney disease progression. Thus, it is hoped that an understanding of the role of inflammation in diabetic kidney disease can add to the choices in therapy in the future.[8-11]

Pathophysiology

Continuous hyperglycemia in blood vessels will result in endothelial damage. This endothelial damage occurs mostly in the capillaries, one of which is in the renal blood vessels. The renal capillary blood vessels will pass through the glomerulus through the afferent blood vessels and out again through the efferent. In passing the afferent to efferent process, glomerular filtration is carried out, the point of which is to filter the blood in the manufacture of urine. In diabetic patients, this endothelial damage causes blood filtering to not take place as it should, so microalbuminuria can be found as a sign of leakage from the glomerulus. In addition, excess blood sugar enters the glomerular cells through the glucose transporter (GLUT) facility, especially GLUT 1, resulting in the activity of several mechanisms such as the poloy pathway, hexoamine pathway, protein kinase C (PKC) pathway, and the accumulation of substances referred to as advanced glycation end-products (AGEs). Several biologically active substances can be found in several experiments, both in vitro and in vivo, which can play an important role in cell growth, cell differentiation, and synthesis of extracellular matrix materials. In the journal obtained, it is said that several growth factors (growth factors) and cytokines play a role in cell proliferation and differentiation and structural and functional changes in the development of diabetic kidney disease. These developmental factors work through a specific cascade and begin with tropic hormones from the hypothalamus that are secreted into the hypothalamus and into the blood circulation and finally reach the endocrine glands in the periphery, causing cell proliferation and differentiation in these organs. Some developmental factors do not directly mediate the effects of these hormones because the effects of some of these organs are mediated by autocrine or paracrine mechanisms.[12-14]

Growth hormone (GH) is a developmental factor associated with diabetes mellitus. In the study, it was stated that dogs that were continuously injected with GH would cause the research object to develop diabetes mellitus. Then, in subsequent studies, it was found that people with diabetes mellitus had higher GH levels than normal people. After that, at almost the same time, a discovery was made that GH contributed greatly to the occurrence of microangiopathy. Also known as insulin-like growth factors (IGFs) are growth factors that work like insulin, namely as a transporter to enter glucose into the tissues. However, in DM patients, it was found that the worsening metabolism in type 1 diabetes mellitus reduced the formation of IGF-I in the liver and reduced the concentration of IGF-I in serum, thus stimulating GH hypersecretion through a feedback mechanism in the hypothalamus. Elevated GH concentrations in circulating blood are believed to stimulate IGF-I formation locally in non-hepatic organs (e.g., kidneys). The GH/IGF system contributes in a complex way to circulatory, extracellular, and most tissues. GH produced by the hypothalamus induces IGF-I synthesis in various organs by activating its Growth Hormone Receptor (GHR) specific, i.e., GH binding protein (GHBP) in humans. After activation of GHR and GHBP by GH/IGF-I, expression is carried out by the mRNA mechanism. In DM patients, serum GHBP

concentrations decrease, and hepatic GHR levels also decrease. In experiments with diabetic rats, significant changes in renal GHR and GHBP mRNA were found on long-term observation. In the first 6 months of observation, no abnormalities were found. However, statistically significant abnormalities were found, namely an increase in the amount of GHBP mRNA in the kidney one month afterward. The changes were seen in the cortex of the kidney, but the changes in the medulla were not too visible. By increasing GHBP mRNA, it will increase the availability of GH in the kidney, thereby increasing cell proliferation and differentiation.[15-18]

In addition, there was also found an increase in transforming growth factor β (TGF-β) in DM patients. TGF-β is a protein that functions to modulate or regulate extracellular matrix production and is believed to also stimulate glomerular mesangial and epithelial cells to produce extracellular matrix proteins, namely proteoglycans, fibronectin, type IV collagen, and laminin. In addition, TGF-β also inhibits collagen synthesis and stimulates tissues to produce metalloproteinase inhibitors. Therefore, TGF-β plays an important role in changing the structure of the extracellular matrix in the event of kidney disorders. In hyperglycemia, it is found that the amount of TGF-β is increased. In the study, it was stated that the amount of glomerular TGF-β1 in rats injected with glucose was found to increase 1 hour after the onset of hyperglycemia. Then, the mice were observed for 2 weeks later and still found an increase in the amount of TGF-β 3 times the initial amount. By increasing the expression of TGF-β mRNA, what is known as diabetes-associated renal hypertrophy. In addition, TGF-β levels were found to remain elevated in diabetic rats 24 weeks later. Because the extracellular matrix increases, the components of the extracellular matrix also increase, namely laminin and type IV collagen. Increased TGF-β in the kidney with diabetes does not occur directly. The increase in TGF-β is stimulated by the activation of the renin–angiotensin system, i.e., in vitro mesangial cells are exposed to angiotensin II. This stimulates TGF-β and the extracellular matrix. In

addition, captopril (ACE inhibitor) was found to reduce the amount of TGF-β and collagen type IV. Protein kinase C (PKC) also plays an important role in diabetic kidney disease. Studies have found that PKC plays an important role in endothelial dysfunction and long-term vascular complications in diabetes. PKC activation in glomerular cells is stimulated by hyperglycemia, which in turn can result in an increase in the amount of TGF-β and mitogen-activated protein (MAP) kinase. In an in vivo experiment giving PKC inhibitors to rats with diabetes for 3 months, it was found that glomerular TGF-β, MAP, and vascular dysfunction (such as increased GFR) decreased. Besides that, the advanced glycation end-product (AGE) inhibitor also decreases the amount of TGF-β in the glomerulus with diabetes. Another developmental factor, i.e., vascular endothelial growth factor (VEGF), has a role in endothelial function in the kidney. In diabetic patients, VEGF expression is stimulated by hyperglycemia, possibly via the PKC pathway. VEGF in the kidney is also stimulated through several other developmental factors, including TGF-β and IGF-I. In a study with diabetic rats with a duration of 3-32 weeks, changes in kidney VEGF concentration were found. This expression is mainly localized to glomerular epithelial cells.[19,20]

Relationship between inflammation and diabetic kidney disease

At the end of the 20th century, the old paradigm of the pathogenesis of diabetic kidney disease was the metabolic and hemodynamic factors caused by diabetes mellitus. After several decades, the deepening of the focus of research on diabetic kidney disease is directed at the molecular pathway. A recent study found inflammatory mediators in the urine of patients with newly recognized and uncomplicated diabetes. The presence of these markers suggests that the inflammatory process plays a role in ongoing kidney damage. It is currently believed that the chronic inflammatory process in the kidney may be the cause of the structural and functional changes in diabetic kidney disease. The mononuclear phagocytic system

in the healthy kidney consists of a collection of cells that express markers specific to interstitial macrophages and dendritic cells. The hemodynamic and metabolic states caused by diabetes, such as hyperglycemia and advanced glycation end products, trigger the release of proinflammatory cytokines and paracrine signals. The predominant cell type infiltrating the kidney is the macrophage. Additional monocytes and macrophages are obtained by uptake by cytokines released by macrophages and other kidney cells. This cycle of cytokine release and recruitment of monocytes and macrophages ultimately leads to the structural changes associated with diabetic kidney disease. The consequences of macrophage infiltration in diabetic kidney disease are the extent of glomerulosclerosis, the degree of tubulointerstitial inflammation, and a decrease in the glomerular filtration rate. Mast cells are another type of acquired immune cell that infiltrates the tubulointerstitium in diabetic kidney disease. Mast cell degranulation releases inflammatory mediators and proteolytic enzymes, such as chymases, which can locally enhance the conversion effect of angiotensin I to angiotensin II. Progression of diabetic kidney disease and decreased glomerular filtration rate are also related to the number and extent of degranulation of mast cells.[21]

The involvement of proinflammatory cytokines in the pathogenesis of diabetic kidney disease is well recognized. Cytokines are a group of polypeptide signaling molecules that trigger autocrine, paracrine, and juxtacrine as part of the acquired immune response. They are secreted from a variety of cells, including T and B lymphocytes, mast cells, macrophages, fibroblasts, stromal cells, and glomerular, endothelial, tubular, and mesangial cells of the kidney. The production of cytokines is affected by several stimuli, such as diabetes, including hemodynamic and metabolic abnormalities. Among the mechanisms most involved in the pathogenesis of diabetic kidney disease are IL-1, IL-6, IL-18, and TNF α Interleukin-I stimulates the production of prostaglandin E and the release of phospholipase A2

and, therefore, has implications for the development of prostaglandin-related intraglomerular hemodynamic abnormalities. Interleukin-I is also associated with increased permeability of vascular endothelial cells. Interleukin-6 plays an important role in the transition from the acquired immune response to the adaptive immune response, concurrent with the influx of neutrophils at the tubulointerstitium. Renal biopsy studies detected the presence of IL-6 mRNA in mesangial, interstitial, and tubular cells, as well as inflammatory cells. In addition to its immune effects, IL-6 may play a role in extracellular matrix dynamics. An increase in the amount of IL-6 can cause hypertrophy and thickening of the glomerular basement membrane and podocyte hypertrophy. Overexpression of IL-6 is associated with albuminuria, and recent studies have shown that serum and urinary IL-6 levels are elevated even before patients experience increased albumin excretion. Interleukin-18 induces the release of interferon γ and other cytokines and increases the expression of adhesion molecules and the induction of endothelial apoptosis. High serum levels of IL-18 were found in patients with macroalbuminuria, which suggests a possible role for IL-18 in the development of renal microvascular complications in diabetes. Early in diabetes mellitus, both tubular and glomerular cells experience increased expression of TNF α mRNA. Serum and urinary TNFα levels were increased in patients with diabetic kidney disease compared to both uncomplicated and non-diabetic diabetic patients, independent of albuminuria. There are several actions of TNF α: induction and differentiation of inflammatory cells, cytotoxicity to several kidney cells including activation and apoptosis, changes in glomerular hemodynamics, increased vascular endothelial permeability, and increased oxidative stress. Tumor necrosis factor-alpha uses a biological mechanism of action through interaction with 2 cell surface receptors, TNF receptor 1 and TNF receptor 2, which shows a promising role as a prognostic biomarker of diabetic kidney disease.[22,23]

Monocyte chemoattractant protein-1

Monocyte chemoattractant protein-1 (MCP-1)/ chemokine (C-C motif) ligand 2 is part of the chemokine group, where MCP-1 is one of the chemokines that was discovered and studied extensively in the last 30 years. Chemokines themselves can be classified structurally into the subfamilies C-X-C, C-C, C-X3-C, and C. Based on the number and location of the cysteine C residue at the N-terminus of the molecule. Chemokines can also be grouped into 2 based on function: inflammatory and homeostatic. The main function of MCP-I is the regulation of inflammatory cells and the control of leukocyte recruitment in inflammation and tissue damage. Chemokines such as MCP-I are secreted in response to signals such as the presence of proinflammatory cytokines and play an important role against monocytes, neutrophils, and lymphocytes. This chemokine is a potent chemotactic against monocytes and plays an important role in several pathophysiological conditions in several organ systems. There are many studies that state the role of MCP-1 in the development of kidney disease. Monocyte chemoprotectant protein -1 has been extensively studied as a potential urine biomarker in several kidney diseases. Once induced, chemokines form chemical ligands for migrating cells that express the appropriate chemokine receptors. Monocyte chemoattractant protein-I is expressed in various cell types. Large amounts of MCP-I are found in endothelial cells, fibroblasts, and mononuclear cells. In the kidney, the cell types that produce MCP-I are tubular cells, smooth muscle cells, mesangial cells, podocytes, and infiltrative cells such as eosinophils and mast cells. The expression of MCP-I is also influenced by the presence of various stimuli. The main inducers of MCP-I are the expression of IL-1, TNF α, interferon-gamma, and several other cytokines. Meanwhile, suppressors of MCP-I are anti-inflammatory molecules such as retinoic acid and glucocorticoids. Unlike its ubiquitous expression, the receptor for MCP-I is more restricted to a few cell types. There are 2 variants of CCR2, including CCR2A, which is expressed by mononuclear cells and smooth muscle cells, while CCR2B is more dominantly expressed by monocytes and cells natural killer activated.[24]

Mechanism of monocyte recruitment by MCP-I

Monocytes are a group of cells circulating in the blood, bone marrow, and spleen and constitute 10% of the total leukocytes. Monocytes originate from the bone marrow and develop through several stages of differentiation. Under certain conditions, monocytes can leave the bone marrow and circulate through the blood to the tissues. Monocytes enter tissues and become macrophages, both in the intestine, lung, and skin. In an inflammatory reaction, the number of monocytes recruited into the bloodstream and into the inflamed tissue increases. Most of these cells give rise to monocyte-derived macrophages as a result of inflammation, whereas the remainder do not differentiate into macrophages and remain as monocyte-like cells, which can migrate to lymph nodes and are called tissue monocytes. In addition to the influx of monocytes from the blood into the tissues during inflammation, all mononuclear cells in the tissues are activated and differentiate into inflammatory cells due to the interaction between pathogens and signaling in the microenvironment. Monocyte chemoattractant protein-1 has 3 different roles. First, MCP-1 recruits monocytes from the bone marrow into the bloodstream. Second, MCP-1 is released at sites of inflammation and stored in the glycocalyx, forming a chemokine gradient and recruiting monocytes to inflamed tissues. Third, locally formed MCP-1 induces cytokine differentiation in monocytes present in tissues. There is also evidence that MCP-1 can attract several other cell types directly to the kidney. Exposure of mesangial cells to MCP-1 induces an increase in inflammatory molecules. In tubular cells, MCP-1 stimulates IL-6 secretion and the formation of ICAM-1. Additionally, on podocytes, MCP-1 binds to the CCR2 receptor.[25]

Monocyte chemoattractant protein-1 in diabetic kidney disease

Diabetic kidney disease has long been seen as a disease with increased fibrosis and hyalinosis and not as a condition caused by inflammation. Chronic kidney disease is characterized by progressive fibrosis that suddenly affects the structure of the kidney, with the final consequence of end-stage kidney disease. Increased accelerated matrix deposition has been reported in the early stages of diabetic kidney disease with or without microalbuminuria. The causes of increased fibrosis from diabetic kidney disease have long been related to the metabolic abnormalities in diabetes. Among other things, the direct effects of glucose and its derivatives of glycosylation end products continued on kidney cells. Inflammation has not been considered the main pathophysiology of diabetic kidney disease until recently. This contrasts with the major role of inflammation in other kidney diseases, where inflammation has always been considered as the main trigger of fibrosis induction. However, recent studies have shown that kidney inflammation is an important part of the development and progression of diabetic kidney disease.[22,24]

Upregulation of MCP-1 may be a major pathway involved in the progression of diabetic kidney disease, in this case, monocyte activation and recruitment in the development of inflammatory kidney disease. The pathogenesis of diabetic kidney disease involves an interaction between metabolic and hemodynamic factors. Hyperglycemia is followed by the withdrawal of monocytes and macrophages, which contribute to the structural and molecular changes that end in glomerulosclerosis. High sugar concentrations stimulate MCP-1 expression in mesangial cells, and high glucose levels rapidly activate NFκB in mesangial cells via reactive oxygen species. In addition, advanced glycated end products (AGEs) induce MCP-1 expression in human mesangial cells. In early 1991, Bohle et al. observed that inflammation of the renal interstitium seen in patients with diabetes contained monocytes, macrophages, T lymphocytes, fibroblasts, and fibrocytes. This finding is supported by Furuta et al., where it was found that the number of macrophages increased significantly in the moderate stage of glomerulosclerosis. Evidence from studies of multiple kidney biopsies suggests macrophage accumulation in diabetic kidney disease predicts a decline in renal function.[23,25]

There are several trials describing the role of MCP-1 in diabetic kidney disease. In experiments on mice with hyperglycemia, MCP-1 deletion was performed, which reduced glomerular and interstitial macrophage infiltration and reduced histological damage. These findings were confirmed by studies in animals with MCP-1 blockade, where there was a reduction of glomerular macrophages by up to 40% and inhibition of the progressive decline in glomerular filtration rate. Recent studies also illustrate that blockade of the CCR2 receptor improves glucose control and kidney damage due to diabetes. These data fueled speculation that blockade of the MCP-1/CCR2 axis may be a new therapeutic target for patients with diabetic kidney disease. Indirect evidence for the hypothesis of an association between MCP-1 and diabetic kidney disease is that in a study examining the effect of intensive insulin therapy on urinary MCP-I and ICAM-I levels, both urine levels were significantly reduced after 2 weeks of intensive insulin therapy. Tamet al evaluated the prognostic value of urinary MCP-I and found that urine levels of MCP-I were higher in patients with microalbuminuria than in patients with normo or microalbuminuria. After period follow-up for 6 years, urinary MCP-I was found to be significantly associated with the rate of change in renal function. In a study with mice with streptozotocin-induced diabetic kidney disease, deletion of MCP-1 protected mice from albuminuria and renal dysfunction. Interstitial and glomerular macrophage infiltration was also reduced with decreased histological damage. In a rat model with type 2 diabetes mellitus, accumulation of glomerular macrophages was found to be associated with the expression of MCP-1 and also associated with the progression of diabetic kidney disease in these mice. In diabetic kidney disease, MCP-1 is produced mostly in the cortical tubules, and this is the same as

in other kidney diseases. Macrophage accumulation around the tubules is associated with tubular damage, and myofibroblast accumulation leads to renal dysfunction.[23,24]

Studies in humans in an experimental study show that macrophage accumulation in the kidney is associated with the progression of diabetes, the development of kidney damage, renal fibrosis, and decreased kidney function, this being the basis for the premise that diabetic kidney disease is a disease mediated by an inflammatory process. In the renal tissue of patients with diabetic kidney disease, MCP-1 can be detected in the tubular cortex, peritubular capillary endothelial cells, and interstitial mononuclear cells. The number of cells with CCR2 as well as urinary MCP-1 levels, reflect the extent and intensity of interstitial fibrosis and tubular atrophy. Urinary MCP-1 levels were significantly higher in patients with diabetic kidney disease than in controls. Urinary MCP-1 levels are associated with albuminuria, and their elevation correlates with the severity of the tubulointerstitial lesion. Many studies show stronger expression of MCP-1 in the interstitium than in the glomerulus. This is related to interstitial changes as well as urinary MCP-1 levels. This illustrates that MCP-I plays an important role in the pathogenesis of diabetic kidney disease, especially in tubulointerstitial lesions. Tubulointerstitial changes are known to be closely related to renal dysfunction. Therefore, elevated urinary MCP-1 levels may reflect the progression of tubulointerstitial damage.[25,26]

2. Conclusion

There is a role for the inflammatory process in diabetic kidney disease. Monocyte chemoattractant protein-1 urine correlated with the progression of diabetic kidney disease both clinically and histologically. Monocyte chemoattractant protein-1 urine can assess the response to therapy and the prognosis of diabetic kidney disease.

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