The Impact of Insulin Resistance and Chronic Kidney Disease on Inflammation and Cardiovascular Disease

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ABSTRACT: There is extensive evidence showing that insulin resistance (IR) is associated with chronic low-grade inflammation. Furthermore, IR has been shown to increase the risk for cardiovascular disease (CVD), even in nondiabetic patients, and is currently considered as a "nontraditional" risk factor contributing to CVD by promoting hypertension, oxidative stress, endothelial dysfunction, dyslipidemia, and type 2 diabetes mellitus. However, chronic kidney disease (CKD) is also considered a state of low-grade inflammation. In addition, CKD is considered an IR state and has been described as an independent risk factor for the development of CVD, as even early-stage CKD is associated with an estimated 40% to 100% increase in CVD risk. There is also strong evidence indicating that inflammation per se plays a crucial role in both the initiation and progression of CVD. Given the above, the combined effect of IR and CKD may significantly increase the risk of inflammation and CVD. This review aims to focus on the complex interplay between IR, CKD, inflammation, and CVD and will present and discuss the current clinical and scientific data pertaining to the impact of IR and CKD on inflammation and CVD.

KEYWORDS: Insulin resistance, chronic kidney disease, inflammation, cardiovascular disease

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Introduction

Insulin resistance (IR) is defined as a reduced biological responsiveness to insulin on glucose uptake at the insulin-sensitive target tissues, such as liver, skeletal muscle cells, and adipose tissue, which creates an imbalance in the glucose metabolism.[1]

There is extensive evidence linking IR with chronic low-grade inflammation[2–4] and the production of several adipocyte-derived pro-inflammatory bioactive proteins, such as tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), resistin, plasminogen activator inhibitor-1 (PAI-1), and monocyte chemoattractant protein-1 (MCP-1), are elevated in IR states.[2,5]

Insulin resistance is associated with increased risk for cardiovascular disease (CVD),[6] even in nondiabetic patients.[7] This disorder is currently described as a "nontraditional" risk factor contributing to CVD by promoting hypertension (HTN), oxidative stress, endothelial dysfunction, dyslipidemia, and type 2 diabetes mellitus (DM2), which are all risk factors of CVD.[8]

Regarding chronic kidney disease (CKD), this condition is considered a state of low-grade inflammation. There is a negative correlation between glomerular filtration rate (GFR) and inflammation, and certain pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, TNF-α, high-sensitivity C-reactive protein (hsCRP), and fibrinogen, tend to progressively increase, along with albuminuria, as kidney function declines.[9]

Chronic kidney disease is additionally described as an independent risk factor for the development of CVD.[10] Even early-stage CKD causes an estimated 40% to 100% increase in the risk of cardiovascular events.[11] "Nontraditional" risk factors seen in CKD, such as increased fibrinogen and albuminuria with resultant low serum albumin levels, have also been linked to CVD.[12] Furthermore, CKD is also considered an insulin-resistant state.[13]

In addition, there is strong evidence indicating that inflammation per se plays an important role in both the initiation and progression of CVD.[14] In that respect, statin therapy has been shown to significantly reduce the risk for CVD, even in patients with minimally only elevated low-density lipoprotein cholesterol (LDL-C) and apparent low risk for CVD in terms of conventional risk factors, by decreasing the hsCRP levels, as well as by reducing the expression of pro-inflammatory cytokines, in addition to lowering LDL-C levels.[15]

Given the above, the combined effect of IR and CKD may significantly increase the risk of inflammation and CVD. This review aims to focus on the complex interplay between IR, CKD, inflammation, and CVD and will present and discuss the current clinical and scientific data pertaining to the impact of IR and CKD on inflammation and CVD.

IR and Inflammation

In addition to their function in fat storage, the adipocytes produce and secrete several bioactive proteins.[16] These cells, and particularly white adipose tissue (WAT), are now recognized as a major site for production of inflammatory cytokines and oxidative stress.[17] During the development of obesity and IR, these cells increase in size and number and their metabolic activity is considerably altered[18]; thus, it becomes easily understandable

that some of the adipocyte-derived factors could play a role in the development of IR.[2]

The lipid accumulation in adipocytes caused by obesity activates c-Jun N-terminal kinase (JNK) and nuclear factor κB signaling pathways that have been associated with an increased production of pro-inflammatory cytokines, such as TNF-α and IL-6, and with the pathogenesis of IR.[2]

Adipocyte tissue macrophages (ATMs) are classified into M1, or classical macrophages with pro-inflammatory effects, and M2, or alternative macrophages with anti-inflammatory effects. In lean individuals, the ATMs are mainly M2 macrophages. However, as obesity develops, there is an increased release of pro-inflammatory adipokines and chemokines that promote the recruitment of M1 macrophages, which in turn further stimulate the release of pro-inflammatory mediators, resulting in obesity-related inflammation and IR.[19]

Among the pro-inflammatory cytokines associated with IR are TNF-α, IL-1β, IL-6, resistin, leptin, PAI-1, and MCP-1.

TNF-α is a pro-inflammatory cytokine, which is overexpressed in the adipose and muscle tissue in obesity and when administered exogenously leads to IR.[20,21] In this regard, acute elevation of TNF-α in plasma causes an increased lipolysis, leading to increased circulatory free fatty acid (FFA) concentration,[22] which has been associated with IR and DM2.[23] Moreover, TNF-α also contributes to IR by impairing insulin signaling via serine phosphorylation of insulin receptor substrate-1 (IRS-1) and of protein phosphatase-1 (PP-1) and by activation of SH-protein tyrosine phosphatase (SH-PTPase).[24]

IL-1β promotes IR by impairing insulin signaling in peripheral tissues and macrophages, thus leading to reduced insulin sensitivity of β-cells and possibly impaired insulin secretion.[25] Studies have also shown a positive correlation between hyperglycemia and IL-1β levels.[26]

Circulating levels of IL-6 are increased in obesity.[27] Chronically elevated levels of IL-6 have been linked to IR.[28] This pro-inflammatory mediator has been described to promote IR by reducing the expression of glucose transporter-4 (GLUT-4) and IRS-1.[29] Furthermore, IL-6 inhibits the metabolism of nonoxidative glucose and also suppresses the lipoprotein lipase that consecutively increases the plasma levels of triglycerides.[30]

Resistin is a small protein produced by murine adipocytes and human peripheral blood mononuclear cells, macrophages, and bone marrow cells. There is extensive evidence suggesting that resistin plays a role in the pathogenesis of obesity, IR, and DM2 in humans.[31]

Leptin mediates appetite and the energy homeostasis. In addition, it limits the accumulation of triglycerides in liver and skeletal muscle, thus improving insulin sensitivity. Furthermore, leptin has glucose-lowering effects by decreasing the hepatic production of glucose.[32,33] However, leptin has been also linked with the progression of IR through a mechanism that is now described as leptin resistance. This condition occurs with obesity and is characterized by increased adipose leptin production without adequate leptin-mediated end-organ response.[34] The impaired regulation of triglycerides, encountered during the leptin resistant state, leads to excess triglyceride accumulation in adipose tissue, as well as to ectopic lipid accumulation, which, as it was mentioned earlier, results in impaired insulin sensitivity and secretion and therefore IR.[2]

PAI-1 is a serine protease inhibitor, which plays a central role in the development of inflammation, obesity, and IR.[35] Moreover, PAI-1 has been linked to IR, even in the absence of obesity.[36] In addition, several studies have established the correlation of PAI-1 with metabolic syndrome, DM2, as well as with vessel wall thickness. Furthermore, higher PAI-1 expression has been observed in coronary artery tissues in the presence of atherogenic lesions, suggesting that PAI-1 may play a role in early atherosclerosis. The association of elevated plasma PAI-1 levels with the incidence of coronary artery disease (CAD) has been reported in several longitudinal studies but this association did not always remain consistent after adjusting for cardiovascular risk factors.[37]

MCP-1 is a chemokine, which has been shown to induce adipocyte dedifferentiation and contribute to pathologies associated with obesity, hyperinsulinemia, and IR, including DM2.[38] There is also strong evidence that MCP-1 plays a major role in atherosclerotic plaque formation, as well as in myocarditis, in cardiac ischemia/reperfusion injury, and in transplant rejection.[39]

However, adiponectin is an insulin-sensitizing protein and is the only adipokine that acts as an anti-inflammatory cytokine. In contrast to the other adipocyte-derived factors, this protein exhibits an inverse association with obesity-induced IR. During insulin-resistant states, plasma adiponectin levels are decreased and adiponectin receptors are downregulated.[40–42] Furthermore, plasma adiponectin levels were found to be significantly lower in patients with CAD than those in age- and body mass index–adjusted control subjects[43] and male patients with hypoadiponectinemia were found to have a significant 2-fold increase in the prevalence of CAD, independent of well-known CAD risk factors.[44] As it was mentioned earlier in this review, CKD is an insulin-resistant state[13]; however, the role of adiponectin in CKD appears to be more complex. In fact, in patients with established CKD, adiponectin levels are actually elevated and, paradoxically, positively predict progression of disease and increased mortality.[45,46] Potential explanations for the increased adiponectin levels in CKD include the loss of balance between the ligand/receptor reactivity, reduced adiponectin clearance by the kidneys leading to impaired biodegradation and abolition, and metabolic derangements in uremia.[46]

A summary of the pro-inflammatory cytokines involved in IR and their actions is shown in Table 1.

IR and CVD

It has been well established that inflammation plays an important role in the development and progression of CVD.[14]

Table 1. IR and inflammation.

PRO-INFLAMMATORY CYTOKINES INVOLVED IN IR	
TNF-α	• Increases lipolysis • Increases circulatory FFA • Impairs insulin signaling
IL-1β	• Impairs insulin signaling • Reduces insulin sensitivity of β-cells
IL-6	• Reduces expression of GLUT-4 and IRS-1 • Inhibits the metabolism of nonoxidative glucose • Increases plasma triglycerides
Leptin (via leptin resistance)	• Impairs regulation of triglycerides • Promotes ectopic lipid accumulation
PAI-1	• Plays a major role in inflammation, obesity, and IR
MCP-1	• Induces adipocyte dedifferentiation

Abbreviations: FFA, free fatty acid; IR, insulin resistance.

Table 2. IR and CVD.

MECHANISMS BY WHICH IR PROMOTES CVD
• Inflammation
• Dyslipidemia
• Increased hepatic triglyceride production
• FFA accumulation
• ROS overproduction/oxidative stress
• Endothelial dysfunction
• HTN due to increased sodium reabsorption

Abbreviations: CVD, cardiovascular disease; FFA, free fatty acid; HTN, hypertension; ROS, reactive oxygen species.

Therefore, IR by promoting inflammation may increase the risk for CVD. Furthermore, as we have mentioned earlier, studies have linked IR to CVD independent to other risk factors, even in nondiabetic patients.[6,7]

Insulin resistance may promote CVD by multiple mechanisms. Insulin resistance promotes dyslipidemia[47,48] and there is a strong positive correlation between hepatic triglyceride production and triglyceride plasma levels in IR, which is independent to body weight.[49] In addition, elevated levels of triglycerides have been also associated with low high-density lipoprotein (HDL) levels, probably via triglyceride enrichment of HDL particles secondary to enhanced cholesteryl ester transfer protein–mediated exchange of triglycerides and cholesteryl ester between HDL and triglyceride-rich lipoproteins, combined with the lipolytic action of hepatic lipase.[50]

Dyslipidemia is defined as elevated blood triglyceride levels and low HDL levels. This lipid pattern is widely considered as an important cardiometabolic risk factor for the development of CVD.[51]

The lipid accumulation, especially FFA accumulation, observed in obesity and IR states, promotes reactive oxygen species overproduction, resulting in oxidative stress,[52] which in turn leads to endothelial dysfunction and atherosclerotic disease.[53]

Furthermore, IR per se promotes endothelial dysfunction.[54] Under normal circumstances, insulin contributes in the maintenance of vascular homeostasis by supporting the production of nitric oxide (NO) by endothelial cells, considered an important vasodilator with anti-aggregatory properties. Moreover, insulin also regulates the vascular smooth muscle growth and migration, as well as the release of endothelin ET-1, which has strong vasoconstrictor properties. However, during IR states, this vascular homeostasis, maintained in part due to the action of insulin, is disturbed, leading to an imbalance in the production and consumption of NO and endothelial dysfunction, resulting in vasoconstriction, vascular smooth muscle cell proliferation, and inflammation.[55] Endothelial dysfunction is considered a predictor of cardiac death, myocardial infarction, and stroke independently to other risk factors.[56]

Insulin resistance has been also linked with HTN, which is one of the main CVD risk factors. Insulin promotes salt reabsorption in multiple nephron segments; therefore, it becomes well understandable that IR, a condition associated with hyperinsulinemia, may further increase sodium reabsorption and consequently may lead to HTN. In addition, as mentioned earlier, the insulin-induced vasodilator effects are impaired during IR.[57] Thus, IR may promote HTN by both sodium imbalance and impaired vasodilation.[58,59]

A summary of the mechanisms by which IR promotes CVD is shown in Table 2.

CKD and Inflammation

Chronic kidney disease, regardless of the primary triggering mechanism, is described as a progressive glomerular, tubular, and interstitial injury with loss of nephron function due to glomerular sclerosis and tubular atrophy.[60] Chronic kidney disease is considered an IR state[13] and thus it can increase the risk of inflammation via IR. However, CKD may also increase inflammation via IR-independent mechanisms.

There is evidence suggesting that CKD may act as a promoter of inflammation in WAT by stimulating an abnormal interaction between macrophages and adipocytes and by promoting an inflammatory response of macrophages to FFA.[61]

Chronic kidney disease is considered a state of low-grade inflammation and it is present in patients with CKD/end-stage renal disease even at young age.[9,62] Furthermore, there is an inverse correlation between GFR and systemic inflammation. Certain pro-inflammatory cytokines such as IL-1β, IL-1 receptor antagonist, IL-6, TNF-α, CRP, and fibrinogen tend to progressively increase, along with albuminuria, as kidney function declines.[9] On this subject, elevated levels of fibrinogen, IL-6 and TNF-α, and low albumin levels have been described as independent predictors of the progression of CKD.[63] Furthermore,

Table 3. CKD and inflammation.

MECHANISMS BY WHICH CKD PROMOTES INFLAMMATION
• CKD is an IR state
• CKD is a state of low-grade inflammation
• Promotes inflammatory response of macrophages to FFA
• Progressive increase in pro-inflammatory cytokines as kidney function declines

Abbreviations: CKD, chronic kidney disease; FFA, free fatty acid; IR, insulin resistance.

CRP and low albumin have been shown to be predictors of morbidity and cardiovascular events in CKD.[64]

A summary of the mechanisms by which CKD promotes inflammation is shown in Table 3.

CKD and CVD

There is extensive, well-established clinical evidence linking CKD to CVD, and individuals with CKD are more likely to die of CVD than to develop kidney failure.[10]

Insulin resistance is very frequent among individuals with CKD[13,65] and it predisposes to systemic inflammation.[61] Thus, through these 2 mechanisms, CKD may likewise increase the risk for CVD. However, CKD is also considered an independent risk factor for the development of CVD[10,66] and this risk increases as the renal dysfunction becomes more severe.[67]

Moreover, CKD has been described as a CAD risk equivalent.[68] Even early-stage CKD causes an estimated 40% to 100% increase in the risk of cardiovascular events.[11]

The association between CKD and CVD is due to the high prevalence of traditional and nontraditional risk factors shared by these 2 conditions. The traditional risk factors observed in both conditions are those that were well described in the Framingham Heart Study, namely, diabetes mellitus, HTN, and dyslipidemia.[69]

Nontraditional cardiovascular risk factors, which are observed particularly in CKD and predispose to CVD, may include increased sympathetic activity, oxidative stress, albuminuria, hyperhomocysteinemia, anemia, CKD-mineral bone disorder with secondary hyperparathyroidism, and inflammation.[70]

Regarding HTN, this condition and CKD are two overlapping conditions, where one can lead to the other and vice versa. Reduced kidney function is associated with HTN, whereas persistent HTN results in renal impairment and can accelerate the progression of CKD.[71] There is an increase in sympathetic activity in patients with CKD, associated with elevated plasma catecholamine levels.[72] In addition, there is an increased sodium retention and increased synthesis of angiotensin II in CKD, resulting in activation of renin-angiotensin system and the development of HTN.[73,74]

Regarding dyslipidemia, during early-stage CKD, there is an imbalance in the lipoprotein metabolism due to an impaired activity of the main enzymes and metabolic pathways, resulting in dyslipidemia and thus leading to an increased risk of atherosclerotic disease in patients with CKD.[75]

Concerning diabetes, which is a major risk factor for CVD,[76] it accounts for up to 40% of prevalent kidney failure and is the leading cause of CKD.[77] Moreover, studies have shown that glycemic control is more difficult to achieve in patients with CKD.[78]

As it was mentioned above, nontraditional cardiovascular risk factors are particularly relevant to patients with CKD and may lead to an increased risk of CVD in those patients. Albuminuria is one of the nontraditional factors associated with CVD in patients with CKD. Even though the mechanisms by which albuminuria contributes to CVD are not well understood, it has been shown that any degree of albuminuria is a risk factor for CVD, even in the absence of diabetes.[79]

With respect to hyperhomocysteinemia, this condition is present in 80% to 85% of patients with CKD[80] and the plasma total homocysteine levels increase as kidney function declines.[81] Hyperhomocysteinemia predisposes to atherosclerotic heart disease by promoting oxidative stress and endothelial dysfunction[82]; therefore, it becomes easily understandable that this condition plays a role in the increased cardiovascular risk in patients with CKD.

Anemia, another nontraditional risk factor that promotes CVD is very frequent in patients with CKD and it worsens as kidney function declines. Anemia is present in about 90% of patients with severe CKD and its presence has been linked to left ventricular hypertrophy, left ventricular systolic dysfunction, and increased cardiovascular morbidity and mortality.[83]

Finally, hyperparathyroidism due to renal impairment (secondary hyperparathyroidism) is another disorder that contributes to the increased cardiovascular risk in patients with CKD. There is a decline in calcium levels as kidney function deteriorates, which is accompanied by increased parathyroid hormone and phosphorus levels.[84] This imbalance, and particularly the associated elevated serum phosphorus levels, has been shown to have a substantial and independent association with all-cause cardiovascular mortality in CKD.[85]

However, CVD also promotes the rapid progression of CKD[86] and is the leading cause of mortality in patients with CKD.[87]

A summary of the factors by which CKD promotes CVD is shown in Table 4.

Conclusions

In summary, the mechanisms leading to immunologic, metabolic, and structural changes observed in IR and CKD are interconnected and have been related to the development of chronic systemic inflammation, leading to functional and structural cardiovascular changes, which may in turn result in atherosclerotic heart disease and eventually life-threatening cardiovascular complications.

Table 4. CKD and CVD.

FACTORS BY WHICH CKD PROMOTES CVD	
Traditional risk factors	• HTN • DM-II • Dyslipidemia
Nontraditional risk factors	• Increased sympathetic activity • Oxidative stress • Albuminuria • Hyperhomocysteinemia • Anemia • CKD-mineral bone disorder

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension.

Author Contributions

CEK conceived the concepts, analyzed the data, jointly developed the structure and arguments for the paper, and made critical revisions and approved final version. DS and CEK wrote the first draft of the manuscript. CT, MDS, PDM, and EG contributed to the writing of the manuscript. CEK, DS, CT, MDS, PDM, and EG agree with manuscript results and conclusions. All authors reviewed and approved the final manuscript.

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