

REVIEW ARTICLE

Insulin Resistance is Associated with Subclinical Vascular Injury in Patients with a Kidney Disease

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Abstract: Patients with kidney disease have a strikingly high cardiovascular risk in the absence of conventional cardiovascular risk factors, including smoking or elevation of cholesterol associated with low-density lipoprotein. Kidney failure remains independently associated with increased cardiovascular risk in patients with diabetes, underlining the specific adverse influence of kidney disease on cardiovascular risk. Vascular injury develops in asymptomatic patients with kidney failure early in the course of the disease. Defective arterial vasodilation, increased arterial stiffness, increased intima-media thickness, and vascular calcification develop in patients with kidney disease long before clinical evidence of cardiovascular events. Even mildly reduced kidney function is associated with a subclinical vascular disease, which is a predictor of worse cardiovascular outcome in patients with kidney failure, similar to the general population and patients with diabetes. Insulin resistance is a typical feature of kidney disease that occurs during the entire span of the disorder, from mild dysfunction to the dialysis phase. Insulin resistance (or its clinical manifestations, the metabolic syndrome or its components) is independently associated with a subclinical vascular injury in patients with kidney disease. Additionally, the risk of developing incident kidney disease and the rapid decline in kidney function is higher in patients with insulin resistance. Animal protein consumption increases dietary acid load and intensifies insulin resistance. Consistently, meat intake promotes diabetes, cardiovascular disease, and kidney failure, while the consumption of plant-based food is protective against the development of the vascular disease. Insulin resistance is a robust cardiovascular risk factor in the general population, patients with diabetes, and patients with kidney disease.

ARTICLE HISTORY

Received: June 25, 2020
Revised: September 16, 2020
Accepted: October 05, 2020

DOI:
10.2174/1573403X16999201210200012

Keywords: Cardiovascular risk, arterial vasodilation, arterial stiffness, pulse pressure, left ventricular hypertrophy, arterial pressure, intima-media thickness, vascular calcification.

1. INTRODUCTION

Prospective studies show that the risk of cardiovascular disease is more elevated in patients with altered Glomerular Filtration Rate (GFR) compared with individuals with normal GFR. The curve that relates GFR and cardiovascular risk is U-shaped, indicating that both reduced GFR (kidney disease) and elevated GFR (glomerular hyperfiltration) increase to the same extent, the risk of cardiovascular events (Fig. 1) [1-9]. Meta-analyses including data from the general population, groups with a high risk of vascular disease, and Chronic Kidney Disease (CKD) cohorts reveal that reduced kidney function is independently associated with cardiovascular disease and all-cause mortality. The Chronic Kidney Disease Epidemiology Collaboration equation categorizes more accurately the risk for mortality and end-stage kidney disease compared to the Modification of Diet in Renal

Disease (MDRD) equation across a broad range of populations [10-13]. The particular importance of CKD as a predictor of cardiovascular disease and all-cause mortality is highlighted by a meta-analysis that shows that the mortality risk is comparable in patients with CKD, irrespective of the presence or absence of diabetes [14]. Consistently, patients with CKD have a higher probability of dying from cardiovascular disease than of progressing to stage 5 and starting renal replacement therapy. In a prospective study that recruited CKD patients with estimated GFR (MDRD equation) between 15 and 90 ml/min/1.73 m², only 3.1% of patients with CKD stage 2-4 progressed to renal replacement therapy while 24.9% died during a 5.5-year observation period. Death was more common than dialysis at all stages [15]. Accordingly, impaired kidney function is independently associated with a vascular injury in a comprehensive histopathologic study of arterial vessels in 100 autopsy subjects [16].

The strikingly high cardiovascular risk associated with CKD is not explained by standard cardiovascular risk factors, but insulin resistance due to activation of glucagon secretion is a typical feature of kidney failure and causes vas-

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cular injury [17]. Insulin resistance is a robust cardiovascular risk factor both in the general population and in patients with previous cardiovascular disease, having been implicated in the occurrence of cardiovascular events in these population groups, independently of other cardiovascular risk factors [18-23]. Diabetes, like CKD, is associated with markedly elevated cardiovascular morbidity and mortality unexplained by hyperglycemia or traditional cardiovascular risk factors such as smoking or hypercholesterolemia. Intensive glycemic control with insulin fails to reduce significant macrovascular complications compared with conventional glycemic control so that cardiovascular disease continues to develop in patients with diabetes despite adequate glycemic control with insulin. In contrast, enhancement of insulin sensitivity with metformin reduces diabetes complications and all-cause mortality in patients with diabetes [24, 25]. Consistently, multiple investigations link insulin resistance with an elevated risk of symptomatic cardiovascular events in patients with type 1 and type 2 diabetes, either lean or obese, independently of other cardiovascular risk factors [26-38]. Further, insulin resistance is independently associated with subclinical vascular disease, including defective vasodilatation, arterial stiffness, intima-media thickening, and vascular calcification in the general population [39-49]. Insulin resistance is also associated with a subclinical vascular injury in patients with diabetes, independently of standard cardiovascular risk factors. Patients with type 2 diabetes experience a long period of insulin resistance before the clinical diagnosis of the disease, unlike patients with type 1 diabetes. Asymptomatic vascular damage injury is not typically present in patients with type 1 diabetes when they are first diagnosed due to insulin deficiency, whereas subclinical vascular injury is evident in patients with screen-detected type 2 diabetes, indicating that insulin resistance has a crucial effect on the development of the vascular disease. Numerous investigations confirm the association between insulin resistance and subclinical vascular disease in patients with diabetes independently of traditional cardiovascular risk factors [47, 50-61]. In addition, insulin resistance contributes to the development of kidney disease in community-dwelling individuals and to the progression of kidney failure in patients with CKD [62-65].

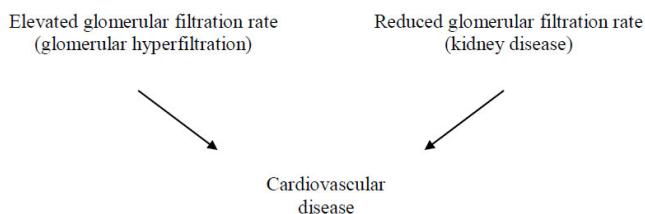


Fig. (1). Both glomerular hyperfiltration and kidney disease are associated with elevated cardiovascular risk to the same extent.

Animal protein consumption, including unprocessed and processed meat (sausages, salami, bacon, hotdogs, ham), has been consistently associated with insulin resistance, assessed by hyperinsulinemic-euglycemic clamps, the homeostasis

model assessment of insulin resistance (HOMA-IR) or the presence of metabolic syndrome or its components (obesity, arterial hypertension, reduced HDL-c, hypertriglyceridemia, glomerular hyperfiltration, microalbuminuria, low urine pH), which are the clinical expression of insulin resistance. The association between animal protein consumption and insulin resistance is independent of body mass index. Weight loss fails to enhance insulin sensitivity in the presence of a diet high in animal products [66-70]. The association between animal protein intake and insulin resistance is particularly apparent during pregnancy, a condition associated with physiological maternal insulin resistance. The intake of unprocessed and processed meat before pregnancy is strongly associated with a higher risk of gestational diabetes, after adjustment for confounders, including body mass index. In contrast, a higher intake of vegetable protein is independently associated with a lower risk of gestational diabetes. Further, the substitution of red meat or processed meat with healthy protein sources, such as nuts or legumes, is associated with a lower risk of gestational diabetes. On the contrary, substituting 5% of energy from vegetable protein with animal protein is associated with a 29% greater risk of gestational diabetes [71, 72].

Accordingly, vegetable food consumption enhances insulin sensitivity, independent of body mass index and other confounding variables. Therefore, replacing sources of animal protein with plant protein improves insulin resistance [22, 66, 67, 69, 70, 73-80].

The aggravation of insulin resistance due to animal protein consumption promotes type 2 diabetes. There is compelling evidence that dietary habits that include animal protein increase the risk of type 2 diabetes, whereas dietary patterns with an elevated content of high-quality vegetable protein contribute to the prevention of the disease. High-quality plant-based foods include nuts, whole grains (rice, wheat, corn), legumes (beans, lentils, soybeans, peas, chickpeas, peanuts), vegetables, and fruits. Accordingly, it has been repeatedly documented that population groups that change their dietary habits from traditional diets rich in vegetable protein to western-type dietary patterns with an elevated content of animal products endure a dramatic increase in the rate of type 2 diabetes mediated by the intensification of insulin resistance [81-89].

Dietary habits have a crucial effect on cardiovascular risk. Consumption of animal products is associated with a markedly increased risk of cardiovascular disease (coronary heart disease, stroke, and peripheral vascular disease), while consumption of plant-based foods reduces the risk of cardiovascular disease, independently of traditional cardiovascular risk factors. There is an inverse relationship between consumption of vegetable food and cardiovascular mortality independently of body mass index and other confounders. Accordingly, population groups that modify their dietary routine, increasing animal products while reducing vegetable food, experience a remarkable escalation in the rate of cardiovascular disease. Investigations that directly compare the effect of animal versus vegetable protein on cardiovascular

risk confirm the differential effect of the two sources of protein. Intake of animal products increases cardiovascular risk, whereas vegetable foods have the opposite effect. Consistently, replacing sources of animal protein with plant protein reduces cardiovascular disease risk [90-94].

In patients with CKD, large prospective cohort studies confirm that dietary habits with elevated consumption of plant-based food enhance insulin sensitivity and are independently associated with lower overall mortality in this population group. A diet rich in legumes, cereals, whole grains, fruits and vegetables, and low in meat and refined sugars is protective from all-cause mortality in patients with CKD, like in the general population, patients with diabetes, and patients with prior cardiovascular disease (Fig. 2) [95-97].

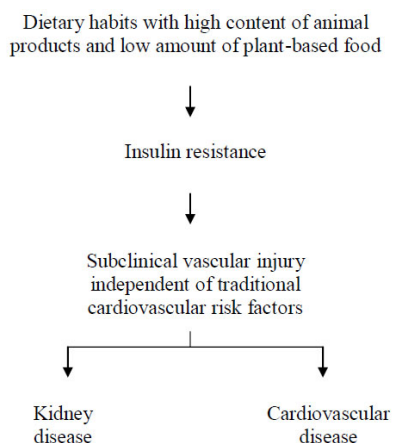


Fig. (2). Insulin resistance is independently associated with kidney disease and cardiovascular disease.

Animal protein ingestion, unlike vegetable protein, activates glucagon secretion. The rise in plasma glucagon associated with animal protein ingestion remains for at least four hours after the intake of animal protein and this response is intensified in patients with diabetes. Other conditions that typically feature hyperglucagonemia include kidney disease, glomerular hyperfiltration, and diabetes [98-100]. Glucagon is the primary hormone that causes insulin resistance. In turn, insulin resistance plays an important role in the development of the vascular disease, although underlying pathogenic mechanisms remain elusive. Glucagon opposes protein synthesis in the skeletal muscle by increasing L-leucine oxidation. This amino acid has a crucial anabolic effect promoting protein synthesis in the skeletal muscle via activation of the kinase target of rapamycin. Glucagon attenuates the anabolic effect of L-leucine by promoting the oxidation of this amino acid. Accordingly, conditions that feature glucagon-induced insulin resistance are typically associated with the blunted ability to synthesize proteins in the skeletal muscle that may result in sarcopenia [101, 102].

Glucagon-induced suppression of protein synthesis in the skeletal muscle increases the availability of amino acids to produce glucose in the liver (gluconeogenesis) [103-105].

The role of the kinase target of rapamycin in the structure and function of the arterial wall is mostly unknown, but inhibitors of this enzyme, such as sirolimus and everolimus, have a beneficial effect on the vascular system. Clinical studies have documented that these agents improve cardiovascular outcomes in patients with coronary disease of native arteries, cardiac allograft vasculopathy, and kidney transplant recipients [106-111].

2. INSULIN RESISTANCE IS ASSOCIATED WITH SUBCLINICAL VASCULAR INJURY IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Patients free of known cardiovascular disease with any degree of CKD experience subclinical vascular damage, including impaired vasodilation, arterial stiffening, increased intima-media thickness of the arterial wall, and vascular calcification (Fig. 3). Subclinical vascular disease in patients with CKD is linked to insulin resistance, while no correlation with conventional cardiovascular risk factors, such as elevated low-density lipoprotein-associated cholesterol (LDL-c), has been found (Table 1). Vascular injury in asymptomatic subjects with CKD is an independent predictor of future cardiovascular events among these patients.

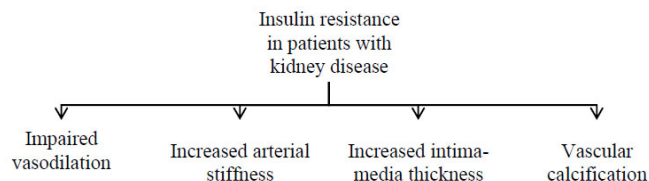


Fig. (3). Insulin resistance is associated with a subclinical vascular injury in patients with kidney disease, independently of traditional cardiovascular risk factors.

2.1. Arterial Vasodilation in Patients with Chronic Kidney Disease

Normal arteries respond with vasodilation to either hyperemia (flow-mediated vasodilation) or administration of acetylcholine, methacholine, sodium nitroprusside, and nitroglycerin (glyceryl-trinitrate). This normal vasodilatory response is impaired in patients with CKD of any degree from mild to the dialysis stage. Both brachial artery flow-mediated vasodilation [112-116] and the vasodilatory response to acetylcholine or methacholine [117, 118] and glyceryl-trinitrate or sodium nitroprusside [112, 113, 117] are attenuated in patients with CKD compared to control subjects, independently of traditional cardiovascular risk factors.

The presence of defective arterial vasodilation increases cardiovascular risk in patients with CKD. In a prospective study with a median follow-up of 41 months, multivariate Cox analysis shows that defective flow-mediated vasodilation predicts cardiovascular outcomes independently of confounders among patients with CKD stages 1-5 [115].

Impaired vasodilation in asymptomatic CKD patients is not justified by smoking or hypercholesterolemia, but severe-

Table 1. Insulin resistance is independently associated with a subclinical vascular injury in patients with chronic kidney disease.

Population Group	Insulin Resistance	Subclinical Vascular Disease	References
Chronic kidney disease (CKD) stage 3-5	HOMA-IR	Decreased brachial flow-mediated vasodilation	[114, 119]
Patients with stage 1-5 CKD	Metabolic syndrome	Reduced brachial artery flow-mediated vasodilation	[120]
Patients with a wide range of renal function	Hypertriglyceridemia Hypertension	Defective arterial vasodilation	[116, 117, 120]
Patients with CKD	HOMA-IR	Increased arterial stiffness	[114, 128, 140]
Patients with CKD	Metabolic syndrome	Increased arterial stiffness	[114, 116, 127-129, 134, 140-142]
Non-diabetic patients with CKD stage 3-5	HOMA-IR	Increased intima-media thickness	[119]
Diabetic and nondiabetic patients with CKD	Metabolic syndrome	Increased carotid intima-media thickness	[143, 144, 146]
Patients on maintenance hemodialysis	Hypertriglyceridemia and reduced HDL-c	Increased carotid intima-media thickness	[129, 143]
Diabetic and nondiabetic patients with CKD	HOMA-IR	Subclinical coronary artery calcification	[157, 185, 186]
Predialysis patients with CKD	Hypertriglyceridemia and reduced HDL-c	Increased coronary artery calcification	[155]
Predialysis patients with CKD	Hypertriglyceridemia and reduced HDL-c	Increased abdominal aortic calcification	[183]
Dialysis patients	Dyslipidemia related to insulin resistance	Increased coronary artery calcification	[168]
Kidney transplant recipients	Metabolic syndrome	Rapid progression of coronary artery calcification	[170, 171, 189, 190]

ral investigations have shown an independent association between insulin resistance and defective vasodilatory response [114, 116, 117, 119, 120]. In nondiabetic patients with stage 3-5 CKD and healthy control subjects, insulin resistance evaluated by the HOMA-IR index is related to decreased brachial flow-mediated vasodilation after adjusting for traditional cardiovascular risk factors [114, 119]. In patients with stage 1-5 CKD, brachial artery flow-mediated dilatation was lower in patients with the metabolic syndrome (the clinical expression of insulin resistance) compared to patients without the metabolic syndrome, suggesting that insulin resistance is associated with defective flow-mediated vasodilation in patients with CKD of any degree [120]. Components of the metabolic syndrome, such as hypertriglyceridemia and hypertension, are independent predictors of defective arterial vasodilation in asymptomatic patients with a wide range of renal function from early-stage CKD to pre-dialysis. However, no correlation with serum cholesterol is observed [116, 117, 120]. In patients with essential hypertension followed-up for 4.5 years in a prospective study, the vasodilatory response to acetylcholine was inversely related with insulin resistance [HOMA-IR values], so that more insulin-resistant patients had reduced vasodilatory response compared with more insulin-sensitive subjects. Impaired vasodilatory response to acetylcholine at baseline was independently associated with progression to type 2 diabetes, suggesting that insulin resistance underlies the defective vascular response [121].

2.2. Arterial Stiffness in Patients with Chronic Kidney Disease

Asymptomatic patients with any stage of CKD experience systemic arterial stiffness independently of standard cardiovascular risk factors, compared to healthy controls [116,

122-128]. Predialysis and dialysis patients endure arterial stiffness to a similar extent [114, 129, 130]. In patients with diabetes, arterial stiffness worsens with kidney failure [131, 132]. The stiffening of the arterial wall increases systolic blood pressure, pulse pressure [systolic blood pressure minus diastolic blood pressure) and cardiac afterload, promoting left ventricular hypertrophy (Fig. 4). Accordingly, patients with CKD have greater systolic blood pressure, pulse pressure, and left ventricular mass compared to control population groups [114, 133, 134].

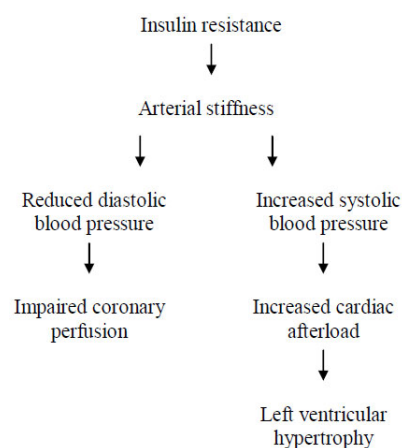


Fig. (4). Simplified cardiovascular consequences associated with arterial stiffness.

Similar to the general population, aortic stiffness is an independent predictor of future cardiovascular events and all-cause mortality in CKD patients. Prospective studies have shown that elevated aortic pulse-wave velocity and pulse

pressure (reflecting increased aortic stiffness) are independent risk factors for all-cause mortality and cardiovascular disease in patients with CKD [135, 136] as well as maintenance hemodialysis [137-139].

Insulin resistance has been associated with subclinical arterial stiffness in patients with CKD. In asymptomatic CKD patients with or without diabetes, several studies have found an independent association between elevated HOMA-IR values and arterial stiffness (increased pulse-wave velocity) [114, 128, 140]. Comparable results are obtained when insulin resistance is ascertained by the presence of the metabolic syndrome or its components. Asymptomatic CKD patients with metabolic syndrome have increased arterial stiffness compared to those without metabolic syndrome [114, 128, 140, 141]. In addition, arterial stiffness is associated positively with age, waist circumference, and blood pressure and negatively with high-density lipoprotein-associated cholesterol (HDL-c) level, independently of confounding variables, in asymptomatic patients with a wide range of kidney dysfunction, suggesting that insulin resistance is a determinant factor of subclinical arterial stiffness in patients with any degree of CKD [114, 116, 127, 128, 140]. The triglyceride-glucose index (calculated as: $\ln[\text{fasting triglycerides (mg/dl)} \times \text{fasting glucose (mg/dl)} / 2]$) has been reported to be a surrogate marker of insulin resistance. In a cross-sectional study including 2,830 participants from the Northern Shanghai Study, multivariable logistic regression revealed that increased triglyceride-glucose index was associated with a higher risk of arterial stiffness, after adjustment for confounders, suggesting that insulin resistance increases the risk of arterial stiffness independently of other cardiovascular risk factors [142]. Insulin resistance (assessed by the HOMA-IR index) is an independent predictor of left ventricular hypertrophy (a sign of arterial stiffness) in a study population of patients with CKD and healthy controls free of cardiovascular disease and diabetes [134]. Patients on hemodialysis are more insulin-resistant (they have reduced HDL-c and elevated triglyceride levels) and show increased arterial stiffness compared to control individuals. However, the two groups have similar smoking habits and LDL-c [129].

2.3. Intima-media Thickness in Patients with Chronic Kidney Disease

The width of the arterial wall can be noninvasively evaluated by ultrasonography usually performed at the carotid artery site. Arterial intima-media thickness is greater in asymptomatic patients with any stage of CKD compared to healthy subjects, independently of standard cardiovascular risk factors. Even a minor deterioration in kidney function is associated with increased carotid intima-media thickness [115, 119, 125, 134, 143-146]. Increased intima-media thickness develops early in the course of kidney disease, having been demonstrated in the carotid artery and the femoral artery in young patients aged 10 to 20 years with stages 2 to 4 CKD [147]. Kidney failure remains an independent risk factor for increased carotid intima-media thickness in patients with type 2 diabetes [144, 148]. Arterial thickening is comparable in predialysis patients with CKD and patients on

chronic hemodialysis. Multiple regression analyses indicate that the presence of renal failure but not being treated with dialysis is associated with increased carotid artery intima-media thickness, independent of other covariates [129, 143, 149].

Like in the general population, longitudinal studies show that subclinical thickening of the carotid wall is a strong predictor of future cardiovascular events and mortality in patients with CKD [150, 151]. Carotid intima-media thickness is also a predictor of calcification of the radial artery in patients with stage 5 CKD (pre-dialysis and hemodialysis), independent of the dialysis status [152].

Traditional cardiovascular risk factors such as hypercholesterolemia or smoking fail to explain the development of subclinical thickening of the arterial wall in CKD patients. However, insulin resistance is independently correlated with increased carotid intima-media thickness in asymptomatic patients with different stages of kidney failure [119, 129, 143, 144, 146]. In asymptomatic nondiabetic patients with CKD stage 3-5, insulin resistance assessed by the HOMA-IR is related to increased carotid intima-media thickness after adjusting for traditional cardiovascular risk factors [119]. In CKD patients with and without diabetes, subclinical carotid intima-media thickness is independently associated with clinical manifestations of insulin resistance, such as arterial pressure and low HDL-c [143, 144, 146].

Patients on maintenance hemodialysis with increased carotid intima-media thickness show elevated triglyceride and decreased HDL-c levels compared to control subjects [129, 143].

2.4. Vascular Calcification in Patients with Chronic Kidney Disease

Vascular calcification is markedly prevalent among asymptomatic patients with any degree of CKD. In these patients, calcification of the arterial wall is widespread across the vasculature and is usually detected non-invasively in the coronary arteries and the abdominal aorta. Vascular calcification begins to develop early in asymptomatic patients with CKD, having been observed in children and young patients [153-155].

Subclinical calcification of the coronary arteries is a common complication of CKD; its prevalence ranges from 40% to 66%. In patients with CKD, coronary artery calcification is more severe and extensive compared to control subjects, frequently affecting more than one coronary artery [153, 155-159]. Several population-based studies, such as the Framingham Offspring Study, the Dallas Heart Study, and the Chronic Renal Insufficiency Cohort Study, have documented a cross-sectional association between kidney failure and subclinical coronary artery calcification, independent of conventional cardiovascular risk factors [160-162]. A similar association between kidney function and coronary artery calcification has been found in a prospective cohort analysis from the Spokane Heart Study, a longitudinal study of community-dwelling adults who were assessed every 2 years for

coronary artery calcification. Multivariate models revealed that reduced kidney function independently predicted coronary artery calcification [163]. Prospective studies reveal that subclinical coronary artery calcification in CKD patients progresses more rapidly compared to subjects with normal kidney function. The faster rate of progression is similar across ethnicities [164-167]. Replacement therapy with dialysis or kidney transplantation does not stop or reverse coronary artery calcification. In young adults with childhood-onset CKD undergoing dialysis, subclinical coronary artery calcification is highly prevalent (92%) and progresses rapidly in the absence of conventional cardiovascular risk factors [154, 168-171].

Prospective analyses show that coronary artery calcification also progresses after kidney transplantation [170]. Autopsy studies reveal that coronary arteries obtained from CKD patients exhibit extensive calcified plaques that occupy a higher proportion of the media compared with subjects without kidney failure. Likewise, the intima-media thickness of the coronary arteries is higher in patients with kidney disease versus control subjects [172-174].

The prevalence of calcification of the abdominal aorta is strikingly high in asymptomatic patients with CKD either prior to dialysis (70.6%-86.3%) or after initiating this procedure (70.8%) [175-179]. In patients with moderate kidney failure (mean estimated GFR of 43.2 ml/min/1.73 m²), the prevalence of subclinical abdominal aortic calcification evaluated by non-contrast computed tomography scan has been reported to be 86.3% [177].

Abdominal aortic calcification evaluated by the scoring system described by Kauppila using a lateral lumbar X-ray is associated with GFR (measured by iothexol clearance). In addition, there is a positive relationship between abdominal aortic calcification and pulse pressure and left ventricular mass, after adjustment for confounders, suggesting that patients with CKD experience wide vascular damage that increases both stiffness and calcification of the arterial wall [179]. The severity and progression of subclinical aortic calcification associated with CKD are greater when diabetes is also present compared to control groups [158, 180].

Prospective studies show that subclinical coronary artery calcification [159, 165, 181, 182] and abdominal aortic calcification [175, 177, 183] are independent predictors of cardiovascular events and all-cause mortality in asymptomatic patients with CKD. In a meta-analysis of prospective studies, subgroup analysis of patients with end-stage renal disease revealed that the presence of calcification in any arterial wall is associated with a 3-4-fold higher risk for cardiovascular events and overall mortality [184].

Subclinical vascular calcification develops in patients with CKD in the absence of traditional cardiovascular risk factors. However, insulin resistance has been independently associated with vascular calcification in asymptomatic patients with any degree of CKD. A number of cross-sectional

studies have shown that insulin resistance evaluated by the HOMA-IR score is an independent risk factor for subclinical coronary artery calcification in diabetic and nondiabetic CKD patients with a broad range of kidney failure. Higher HOMA-IR values are positively associated with a greater prevalence of subclinical coronary artery calcification in patients with CKD, after adjustment for cardiovascular risk factors [157, 185, 186]. Clinical features of insulin resistance, such as high triglyceride level, has been identified as an independent determinant of coronary artery calcification [155] and abdominal aortic calcification [183] in patients with CKD. In patients with diabetes and CKD, vascular calcification is more severe, suggesting that insulin resistance, which is typically present in the two conditions, may be an underlying common cause of vascular injury [158, 161, 167, 175, 180, 187, 188]. In patients on dialysis, a prospective study shows that coronary artery calcification progresses over time compared to baseline values. Rapid progression of coronary artery calcification is associated with high triglyceride and low HDL-c concentration (dyslipidemia typically related to insulin resistance), while no correlation with other lipid levels could be found [168]. Prospective cohort studies in renal transplant recipients with no prior history of cardiovascular disease reveal that clinical features of insulin resistance, such as the metabolic syndrome, high triglyceride level, and elevated arterial pressure, predict rapid progression of coronary artery calcification, independently of confounding variables. However, an association of coronary artery calcification with LDL-c was not identified. The prevalence of coronary artery calcification at baseline was higher in more insulin-resistant recipients compared with insulin-sensitive participants [170, 171, 189]. Consistently, metabolic syndrome is an independent cardiovascular risk factor in renal transplant recipients in a prospective study with an 8-year follow-up. Recipients with the metabolic syndrome at baseline (1 year after transplant) had an increased risk of cardiovascular events at follow-up compared with those without the metabolic syndrome [190].

3. INSULIN RESISTANCE IS A RISK FACTOR FOR THE DEVELOPMENT AND PROGRESSION OF KIDNEY DISEASE

Systemic vascular injury associated with insulin resistance may affect kidney vasculature to induce kidney damage in the general population and to accelerate the loss of kidney function in patients with CKD (Table 2). Dietary patterns with an elevated content of animal protein and a low amount of plant-based food induce insulin resistance and contribute to the deteriorating kidney function.

3.1. Insulin Resistance Increases the Risk of Developing Kidney Disease in the General Population

Both cross-sectional and prospective observational investigations show that insulin resistance is a risk factor for developing kidney disease in the general population, independently of confounding factors.

Table 2. Insulin resistance is independently associated with an increased risk of kidney disease and the progression of kidney failure.

Type of Study	Population Group	Insulin Resistance	Risk of Kidney Disease	Reference
Cross-sectional	General population US	HOMA-IR	Strong association between insulin resistance and the risk of kidney disease	[191]
Cross-sectional	General population US	Metabolic syndrome	Strong relation between metabolic syndrome and the risk of kidney disease	[192]
Cross-sectional	1,678 non-diabetic subjects	HOMA-IR	HOMA-IR was associated with reduced kidney function	[194]
Cross-sectional	General population	Metabolic syndrome	Graded relation between metabolic syndrome and kidney disease	[193]
Cross-sectional	Kidney transplant	Metabolic syndrome	Insulin resistance is associated with impaired allograft function	[202]
Prospective	General population	Metabolic syndrome	Association between metabolic syndrome and kidney disease	[201]
Prospective	Community-based cohort	Hyperinsulinemic euglycemic clamp	Insulin resistance is associated with new-onset kidney disease	[197]
Prospective	Community-based cohort	HOMA-IR	HOMA-IR is associated with the risk of developing kidney disease	[204]
Prospective	General population	Metabolic syndrome	Progressive relation of metabolic syndrome and kidney disease	[206]
-	-	-	Risk of kidney disease progression	-
Prospective	MDRD study	Metabolic syndrome	Blood pressure and HDL-c predicted progression of kidney failure	[213]
Prospective	ARIC study	Dyslipidemia of insulin resistance	Dyslipidemia of insulin resistance predicted decline in renal function	[214]
Prospective	Patients with kidney disease	Metabolic syndrome	Metabolic syndrome increases the risk of kidney failure progression	[216]
Prospective	Patients with kidney disease	HOMA-IR	Higher HOMA-IR predicts worsening of kidney function	[218]

Insulin resistance or its clinical features are strongly and independently associated with an increased prevalence of CKD in large community-based cross-sectional studies [191-193].

In 2003, the cross-sectional relationship of insulin resistance to the risk of prevalent CKD was examined among nondiabetic participants of the Third National Health and Nutrition Examination Survey (NHANES III), conducted between the years 1988 and 1994. CKD was defined as an estimated GFR < 60 ml/min/1.73 m², calculated by the MDRD formula. The prevalence of CKD was progressively higher with increasing levels of serum insulin and HOMA-IR after adjustment for confounding variables. A strong, positive, and dose-response association between insulin resistance and risk of CKD among nondiabetic individuals from the US general population was observed [191]. A similar result has been obtained in another population group. HOMA-IR was associated with the likelihood of reduced kidney function in a cross-sectional analysis of 1,678 subjects without diabetes [194]. In 2004, the cross-sectional association between the metabolic syndrome and risk for CKD was examined in the NHANES III study, which confirmed the previous results. Kidney failure was defined as an estimated GFR < 60 ml/min/1.73 m², calculated by the MDRD equation. A strong, positive, and independent relationship between metabolic syndrome and risk for prevalent CKD was identified. In addition, the risk for kidney disease increased progressively with a higher number of components of the metabolic syndrome after adjustment for confounding variables [192]. A similar graded relationship between increasing components of the metabolic syndrome and augmented

prevalence of CKD has been confirmed in the NKF (National Kidney Foundation) Kidney Early Evaluation Program study [193]. The association between insulin resistance and increased prevalence of CKD is consistent across ethnic groups, including American Indians and population groups from Japan, Thailand, Sweden, and China [195-201]. In renal transplant recipients, a cross-sectional study shows that clinical manifestations of insulin resistance such as systolic blood pressure and hypertriglyceridemia are independently associated with impaired allograft function beyond one year post-transplant, after adjustment for established risk factors [202]. Diet is a major determinant of the acid load that must be excreted by the kidney to maintain acid-base balance. Dietary habits with a high content of meat, fish, and cheese and low content of legumes, vegetables, and fruits typically increase the dietary acid load and intensify insulin resistance. The association of dietary acid load with kidney disease was examined among 12,293 participants in the NHANES 1999-2004. The dietary acid load was assessed by estimating net acid excretion from nutrient intake and body surface area. Kidney disease was defined as estimated GFR < 60 ml/min/1.73 m², calculated by the MDRD equation. The higher dietary acid load was independently associated with kidney failure [203].

Insulin resistance is an independent predictor of incident kidney disease in longitudinal studies, evaluated either by the hyperinsulinemic-euglycemic clamp [197] or by the HOMA-IR index [201, 204]. Higher insulin resistance at baseline is associated with a greater risk of new-onset kidney disease during follow-up independently of confounding factors, suggesting that insulin resistance is involved in the develop-

ment of kidney failure at an early stage. Community-based prospective studies involving different ethnic groups have consistently documented an independent association between baseline components of the metabolic syndrome and the risk of developing CKD at follow-up. Additionally, the risk for incident CKD increases progressively with a higher number of components of the metabolic syndrome at baseline, after adjustment for confounding factors [196, 198, 201, 204-210]. The prospective relationship between dietary protein sources and dietary acid load with incident CKD was evaluated in the Atherosclerosis Risk in Communities study among participants without baseline CKD. Red and processed meat consumption [high dietary acid load that increases insulin resistance] is associated with a greater risk of developing incident CKD. In contrast, higher dietary intake of nuts and legumes is associated with a lower risk of new-onset kidney disease in this community-based sample [211, 212].

3.2. Insulin Resistance Accelerates the Decline of Kidney Function in Patients with Chronic Kidney Disease

In addition, prospective studies show that insulin resistance predicts the decline of kidney function in patients with CKD independently of other risk factors.

Longitudinal studies show that insulin resistance [evaluated by its clinical manifestations or the HOMA-IR index] contributes to the progression of renal disease in patients with CKD.

In 1997, the MDRD study investigated baseline factors that predicted the decline of kidney function in patients with CKD. The renal clearance of ¹²⁵I-iothalamate was used to measure GFR. Higher arterial pressure and lower HDL-c were independent predictors of progression in patients with GFR between 25 and 55 ml/min/1.73 m² [213]. The Atherosclerosis Risk in Communities study obtained a comparable result in 2000. Among 12,728 participants with baseline serum creatinine less than 2 mg/dl in men and less than 1.8 mg/dl in women, higher triglycerides and lower HDL-c at baseline predicted a future decline in renal function independently of confounders over 2.9 years of follow-up. These associations were significant in participants with and without diabetes. In contrast, LDL-c had no predictive value concerning the loss of kidney function [214]. Consistently, prospective cohort studies reveal that the occurrence of metabolic syndrome is an independent determinant of CKD progression. Patients with CKD and metabolic syndrome have a higher risk of progression than those CKD patients without metabolic syndrome. In addition, the risk of a rapid decline in GFR increases gradually with the increase in the number of metabolic syndrome components [201, 204, 215, 216]. Comparable findings have been obtained when insulin resistance is evaluated by the HOMA-IR index. Insulin resistance is an independent predictor of kidney function loss in longitudinal studies. A higher HOMA-IR value at study entry independently predicts the deterioration of kidney function in CKD patients [199, 204, 217, 218]. The prospective association between dietary acid load and progression of CKD to end-stage kidney disease was investigated in partici-

pants of the NHANES III over a median of 14.2 years of follow-up. The dietary acid load was quantified by net acid excretion. In the fully adjusted model, a higher dietary acid load was associated with an increased risk of end-stage kidney disease. Animal protein consumption increases dietary acid load and induces insulin resistance [219].

CONCLUSION

It has been long known that patients with kidney disease endure a remarkably elevated cardiovascular risk compared to the general population. The detrimental effect of kidney failure on vascular disease is present in patients with and without diabetes. Patients with kidney disease are more likely to die from a cardiovascular cause than to reach replacement therapy. Insulin resistance is a characteristic manifestation of kidney disease that occurs throughout the course of the disorder. Like in healthy subjects and patients with diabetes, insulin resistance is independently associated with a subclinical vascular injury in patients with kidney disease. Impaired vasodilation, arterial stiffness, arterial wall thickening, and vascular calcification develop in patients with kidney disease in the absence of cardiovascular risk factors and predict cardiovascular outcomes. Additionally, insulin resistance contributes to the development of kidney disease in the general population and to the progression of kidney failure in patients with CKD. Dietary patterns with high animal protein consumption and low intake of vegetable food intensify insulin resistance and promote diabetes and vascular injury. Animal protein consumption has been linked to subclinical vascular disease in patients with kidney failure, diabetes, and healthy subjects. Insulin resistance is a cardiovascular risk factor in the three conditions.

HIGHLIGHTS

- Cardiovascular risk is markedly elevated in patients with chronic kidney disease.
- In kidney disease, cardiovascular risk is not linked to standard cardiovascular risk factors.
- Subclinical vascular damage develops early in the course of chronic kidney disease.
- In patients with kidney failure, subclinical vascular injury predicts cardiovascular events.
- Insulin resistance occurs throughout the whole course of kidney disease.
- Subclinical vascular disease is associated with insulin resistance in kidney disease.
- Animal protein consumption worsens insulin resistance and promotes vascular damage.

LIST OF ABBREVIATIONS

CKD	= Chronic Kidney Disease
GFR	= Glomerular Filtration Rate

HDL-c = High-Density Lipoprotein-associated Cholesterol
 HOMA-IR = Homeostasis Model Assessment-Insulin Resistance
 LDL-c = Low-density Lipoprotein-associated Cholesterol
 MDRD = Modification of Diet in Renal Disease
 NHANES = National Health and Nutrition Examination Survey

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We are very grateful to Ms. Gema Souto for her continuous support.

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