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Review

Insulin Resistance in Kidney Disease: Is There a Distinct Role Separate from That of Diabetes or Obesity?

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Abstract
Insulin resistance is a central component of the metabolic dysregulation observed in obesity, which puts one at risk for the development of type 2 diabetes and complications related to diabetes such as chronic kidney disease. Insulin resistance and compensatory hyperinsulinemia place one at risk for other risk factors such as dyslipidemia, hypertension, and proteinuria, e.g., development of kidney disease. Our traditional view of insulin actions focuses on insulin-sensitive tissues such as skeletal muscle, liver, adipose tissue, and the pancreas. However, insulin also has distinct actions in kidney tissue that regulate growth, hypertrophy, as well as microcirculatory and fibrotic pathways which, in turn, impact glomerular filtration, including that governed by tubuloglomerular feedback. However, it is often difficult to discern the distinct effects of excess circulating insulin and impaired insulin actions, as exist in the insulin resistance individual, from the associated effects of obesity or elevated systolic blood pressure on the development and progression of kidney disease over time. Therefore, we review the experimental and clinical evidence for the distinct impact of insulin resistance on kidney function and disease.

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Introduction

Insulin resistance is an integral component of a constellation of metabolic and hemodynamic abnormalities that places individuals at risk for progression to type 2 diabetes, but importantly also places one at heightened risk for cardiovascular disease and chronic kidney disease (CKD). Distinct and separate from diabetes, the presence of insulin resistance and compensatory hyperinsulinemia is strongly associated with the presence of CKD stages 1–4 [1–3], and constellates with other abnormalities such as obesity, hypertension, and dyslipidemia, e.g., cardiorenal metabolic syndrome [4–7] (Fig. 1). However, in population studies and experimental models it can be difficult to discern the distinct and separate kidney effects of insulin resistance and the associated hyperinsulinemia from the impact of overt diabetes with hyperglycemia, visceral adiposity seen in obesity, and the presence of vascular stiffness and elevated systolic blood pressure. Given this, we will review the importance of insulin resistance and excess circulating insulin in the pathogenesis of kidney dysfunction and injury separate from that of hyperglycemia and obesity.

Mechanisms of Insulin Resistance and Impact of Insulin on the Kidney

Our conventional understanding of tissue insulin resistance is that it constitutes an underlying impairment in the response of a target organ, such as skeletal muscle, to the metabolic actions of insulin [8, 9]. There are insulin-sensitive tissues such as skeletal muscle, liver, pancreas, and adipose tissue as well as cardiovascular and kidney tissue. Resistance to the metabolic actions of insulin in these nontraditional tissues contributes to heart, vasculature, and kidney structure and function, independent of the alterations in glucose disposal and systemic insulin sensitivity. Indeed, insulin metabolic signaling in these tissues regulates cardiovascular remodeling and blood pressure via effects on the sympathetic nervous system, the renin-angiotensin-aldosterone system, and intrarenal regulatory mechanisms.

The most studied pathway regarding insulin-dependent metabolic signaling for glucose utilization involves insulin receptor substrate 1 (IRS-1) engagement of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway in skeletal muscle as well as adipose and liver tissue [8]. In the context of insulin resistance, there are a number of mechanisms thought to contribute to the impaired responses to insulin. Most abnormalities are characterized either as a prereceptor, receptor, or postreceptor signaling defects [5, 8, 9]. However, the bulk of work to date has focused on impaired signaling at the insulin receptor and postreceptor levels, i.e., altered insulin receptor/IRS-1/PI3K/Akt signaling and reductions in glucose transport/uptake.

Very briefly, insulin-dependent binding of insulin receptor in a normal physiologic state autophosphorylates the beta subunit and then undergoes rapid phosphorylation by tyrosine of IRS-1. IRS-1 docking proteins then bind to PI3K via an SH-2 domain with the p85 subunit of PI3K. PI3K/Akt activation is critical not only in traditional insulin-sensitive tissues, but also in cardiovascular and kidney tissue in transduction of insulin-dependent responses [5, 10]. Further, PI3K/Akt activation mobilizes GLUT4 to the plasma membrane, which then facilitates glucose uptake and utilization. Disruption of this signaling pathway leads to resistance to the metabolic actions of insulin that results in a compensatory increase in circulating insulin (e.g., hyperinsulinemia). It is especially important to note that while hyperinsulinemia may compensate for this resistance to tissue insulin actions, the excess insulin may result in insulin-dependent growth pathway activation in tissues with normal or minimally impaired insulin sensitivity, such as in the kidney [10–13].

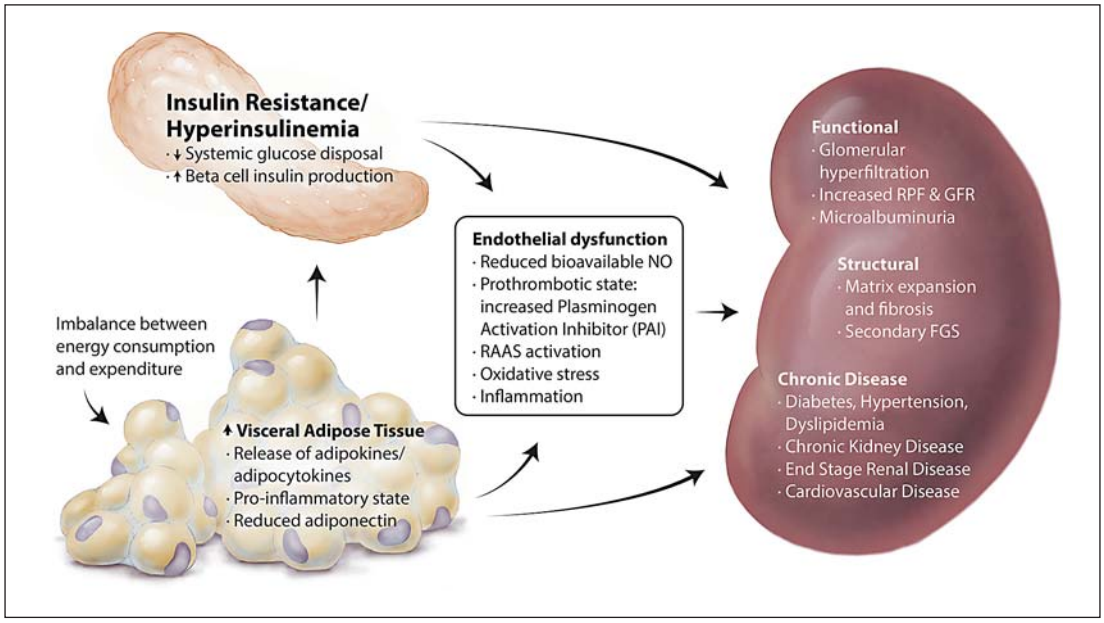

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Fig. 1. The distinct role for insulin resistance and insulin actions in the kidney. The development of hyperinsulinemia in insulin resistance has a role in the development of kidney injury separate from that of obesity and the development of type 2 diabetes. FGS, focal glomerulosclerosis; GFR, glomerular filtration rate; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; RPF, renal plasma flow.

The compensatory increase in insulin-resistant states has a number of maladaptive consequences on cardiovascular and, importantly for this review, kidney tissue. In this context, the routine metabolic signaling that regulates insulin-dependent glucose transport/utilization can occur in opposition to growth signaling pathways that are also dependent on insulin. These pathways include serine kinases that are redox-sensitive, including extracellular receptor kinase, Rho kinase, JUN NH_2-terminal kinase, and the mammalian target of rapamycin/serine kinase 1 signaling pathways [11–17] that regulate growth, hypertrophy, and fibrotic pathways. These pathways are also under the control of other neurohumoral pathways in insulin-resistant states, i.e., the sympathetic nervous system and the renin-angiotensin-aldosterone system [10, 18, 19]. Both angiotensin II and aldosterone promote activation of various kinases that are redox-sensitive, such as serine kinase 1 that promotes growth and hypertrophy pathways that ultimately lead to kidney tissue remodeling [10, 16–21].

Beyond promoting glucose uptake and utilization, insulin-dependent PI3K/Akt activation also phosphorylates/activates endothelial nitric oxide (NO) synthase which in turn increases bioavailable NO in the vascular endothelium [22–24]. Thus, under conditions of tissue resistance to insulin, the alterations in insulin-dependent responses of the PI3K/Akt pathway lead to reductions in bioavailable NO, impaired NO-dependent vascular relaxation, and increased tissue inflammation and fibrosis. These effects occur in parallel to a reduction in glucose uptake and utilization. In the context of renal glomerular hemodynamics, this impairment in insulin metabolic signaling and reduction in PI3K/Akt due to insulin resistance promotes reduced NO production and associated impairment of tubuloglomerular feedback, hyperfiltration, and sodium retention [25–30]. Tubuloglomerular feedback is the mechanism by which the kidney autoregulates renal blood flow and glomerular filtration. It is also important to understand that reduced bioavailable NO has other adverse effects on kidney

vessels such as leukocyte and monocyte recruitment, platelet aggregation, and adhesion among other proinflammatory effects.

Therefore, it is increasingly clear that insulin has a distinct role in the kidney through regulation of metabolic and growth pathways as well as the kidney microcirculation, and ultimately impacts renal plasma flow, glomerular filtration, and tissue inflammation and fibrosis.

Insulin Resistance and CKD: Population Level Evidence

One of the earliest studies to suggest that there existed a unique relationship between insulin resistance and kidney disease employed hyperinsulinemic, euglycemic clamps in nondiabetic CKD subjects and compared the glucose disposal rate compared to controls [31]. For the first time, the presence of systemic insulin resistance in uremic CKD patients without clinical diabetes was observed. Over time, a number of other groups made similar observations regarding the development of insulin resistance at various stages of CKD independent of the presence of type 2 diabetes [32–34]. In one study of a mixed CKD population (e.g., diabetic kidney, IgA nephropathy, polycystic kidney disease, etc.), insulin resistance was evident in earlier stages of CKD, and yet there were no differences in insulin sensitivity measures between the populations. This observation suggests that CKD itself, rather than the underlying specific disease process, was driving the systemic insulin resistance [35]. Importantly, data from another study reported that glucose disposal, as a measure in the hyperinsulinemic clamp technique, was reduced in CKD patients compared to healthy controls [36]. This reduction in glucose disposal was influenced by the presence of acidosis and APO A1B levels, but not glomerular filtration rate (GFR); however, there was a strong relationship between the glucose disposal rate (e.g., insulin sensitivity) and creatinine clearance. Indeed, when compared to early stages (e.g., CKD stage 1 and 2), insulin sensitivity measures were more reduced in patients with CKD stage 3 [37].

This graded relationship between increasing impairments of renal function and insulin metabolic actions is an important observation that underscores the findings from a number of database studies that support a strong correlation between insulin resistance and CKD independent of type 2 diabetes [38–40]. Early data suggested that there was a strong relationship between microalbuminuria and systemic insulin resistance; further, this relationship was inverse as increases in albuminuria were related to reductions in insulin sensitivity [38]. Subsequent findings derived from a secondary analysis of composite registry data, after controlling for diabetes, indicated that insulin resistance conveys an increased risk for progression of CKD to end-stage renal disease (ESRD) [41]. Data from cohort analyses including the National Health and Nutrition Examination Survey and the National Kidney Foundation's Kidney Early Evaluation Program extended these findings, suggesting that there exists a strong relationship between CKD and insulin resistance independent of type 2 diabetes [1, 38, 39]. However, these studies also demonstrate that the relationship was stronger in the presence of obesity. A number of studies looking at this relationship between insulin resistance and CKD made the important observation that the relationship occurred in a graded fashion that was strengthened by increasing components of the metabolic syndrome such as central obesity, hypertension, and the presence of metabolic dyslipidemia [1, 38].

While it is clear then there exists a relationship between insulin resistance and CKD, a number of studies have reported confounding data between insulin sensitivity, CKD, and the presence of obesity.

What Is the Role of Obesity in CKD/ESRD Separate from That of Insulin Resistance?

There is a general consensus that overnutrition and the development of obesity is a pandemic that further drives an increased risk for metabolic complications including insulin resistance and overt type 2 diabetes, elevations in systolic blood pressure, and dyslipidemia. This constellation of metabolic disorders can make it difficult to discern the individual contributions of each component on kidney disease in both experimental and clinical models. Data from the World Health Organization suggest that there are over a billion overweight and obese adults. The obesity trends observed over the past several decades have been occurring in parallel with the expansion of the ESRD population. In this regard, among incident ESRD patients there are continued increases in mean weight and body mass index (BMI) of those with and without diabetes, respectively [42, 43]. During this time period, there have been a number of other database studies that support a causal association between BMI and predialysis CKD [43–45]. One study that employed a population-based case-control cohort design suggested that there was an increased risk for those overweight with a BMI ≥25 for CKD (estimated GFR <60 mL/min/1.73 m^2) compared to those with a BMI ≤25 [45]. The relationship for an increased risk for CKD held true at higher BMI levels (≥30 in males and then ≥35 even after adjusting for the presence of diabetes over a lifetime). When looking at earlier-stage CKD in those with an estimated GFR >60 mL/min/1.73 m^2, another study derived from a passive secondary analysis of a community-based population supported the notion that incident CKD in obesity is driven solely by the relationship with BMI and proteinuria [41].

As described above, increased BMI and obesity are not only associated with incident CKD, but are also highly prevalent in ESRD. Considering this, there are data suggesting that the presence of obesity (BMI >30) paradoxically confers a survival advantage in ESRD rather than being a risk factor for cardiovascular disease morbidity and mortality in this population [46]. Further, there are a number of population studies that indicate that a lower BMI (<25) is a consistently strong predictor of increased mortality, a relationship that is lost at higher BMIs [47–51]. It is thought there may be significant residual confounding in these studies due to unmeasurable variables such as the lack of time-dependent assessment of nutritional indices, progressive malnutrition, protein energy wasting, uremic conditions, or the presence of residual renal function in the end-stage kidney that cannot be accounted for in these population-level studies. It is also important to note that these studies were done in ESRD populations and do not account for the impact of obesity on the development and progression of CKD.

In the context of the impact of obesity on the development and progression of CKD, there has been work evaluating the role of obesity in ESRD progression from a large historic cohort that included those with an increased BMI and established CKD [52]. In this study, the presence of a BMI >25 predicted the progression of CKD to ESRD, and the relationship was graded with increases in BMI and risk for ESRD independent of the presence of diabetes and hypertension. Data from a number of other cohort studies also suggest that obesity contributes to the development of proteinuria. In one prospective cohort followed after unilateral nephrectomy, those with established obesity (BMI ≥30) had a higher rate of incident albuminuria and CKD [53]. In the general population, data from the Prevention of Renal and Vascular End Stage Disease study suggest that the majority of incident microalbuminuria occurred in those overweight persons with a BMI ≥25 without presence of either diabetes or hypertension [54, 55].

These collective data support the concept that obesity not only contributes to progressive loss of kidney function in those with established kidney disease, but also elicits loss of kidney function in healthy subjects independent of insulin resistance.

Impact of Obesity on the Kidney Distinct from That of the Presence of Insulin Resistance and Hyperinsulinemia

The traditional early view of the detrimental effects of obesity on the kidney focused on physical compression of fat tissue on the kidney and the consequent alteration of intrarenal hemodynamics. In this regard, it is known that obesity also influences intrarenal hemodynamics through affecting renal plasma flow and GFR (e.g., hyperfiltration) that contribute to albuminuria over time independent of the effects of hyperinsulinemia as seen in insulin resistance [56–62]. The increased GFR associated with a high renal plasma flow is the result of an increased transcapillary pressure gradient and dilated glomerular afferent arterioles [57, 58]. This mechanism of hyperfiltration is then enhanced by proximal tubule sodium reabsorption, resulting in a reduction in salt delivery to the macula densa and thereby diminished tubuloglomerular feedback [56–62]. The hyperfiltration observed then contributes over time to kidney tissue remodeling through basement membrane thickening and mesangial sclerosis, findings that are similar to those seen in early diabetic kidney disease (e.g., focal glomerulosclerosis) [62]. This glomerular mesangial expansion observed in obesity is referred to as an obesity-associated secondary form of focal segmental glomerulosclerosis [62].

It is important to note that our understanding of obesity and its impact on the kidney has evolved in recent years, and that emerging data support the notion that there is a link between an inflamed adipose tissue and the development of kidney injury in obesity. It is now thought that adipose tissue is a metabolically active organ that has a direct impact on the kidney through production of inflammatory adipocytokines such as resistin, tumor necrosis factor α, and interleukin-6. Enhanced production of adipocytokines is increasingly recognized to be promoting kidney disease associated with obesity [57, 58, 63]. For example, there is evidence for a hypothalamus selective resistance to the metabolic actions leptin while its sympathetic nervous system activation effects on organs such as the kidneys are maintained [59]. The proinflammatory adipocytokine tumor necrosis factor α has been shown to promote macrophage recruitment and infiltration with consequent glomerular and tubulointerstitial inflammation as well as to promote upregulation of other inflammatory cytokines which promote kidney tissue fibrosis [64–68]. On the other end of the spectrum in obesity, there is a reduction in the anti-inflammatory adiponectin, and this reduction is associated with increases in albuminuria as well as kidney tissue fibrosis [62, 65].

Conclusions

In summary, it is clear that presence of the cardiorenal metabolic syndrome contributes to kidney injury and ultimately CKD. Experimental and clinical evidence support this relationship. In this regard, both insulin resistance and excess visceral adiposity contribute to maladaptive mechanisms in the kidney, including reductions in bioavailable NO that elicit attenuated tubuloglomerular feedback, hyperfiltration, and increased renal tubule sodium retention. They also promote glomerular mesangial expansion, glomerular hypertrophy, and kidney fibrosis that lead to the development of hypertension and albuminuria, all of which promote progression of kidney disease. Experimental models have dissected out the distinct pathways unique to both hyperinsulinemia (e.g., insulin resistance) and excess visceral adiposity (e.g., obesity) that contribute to kidney injury and disease. However, the clinical evidence is less clear. Smaller physiologic studies suggest a very real and direct negative renal impact of insulin resistance/hyperinsulinemia in eliciting kidney disease and vice versa. Yet, when looking at larger-database and prospective cohorts, it is less clear that there

is a distinct role for insulin resistance independent of coexisting obesity or diabetes. Therefore, there is much work to be done to understand the metabolic relationships with CKD.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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