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Measurement of insulin resistance in chronic kidney disease

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Abstract

Purpose of review—Insulin resistance is a known complication of end-stage renal disease that also appears to be present in earlier stages of chronic kidney disease (CKD). It is a risk factor for cardiovascular disease and an important potential therapeutic target in this population. Measurement of insulin resistance is reviewed in the context of known pathophysiologic abnormalities in CKD.

Recent findings—Insulin resistance in CKD is due to a high prevalence of known risk factors (e.g. obesity) and to unique metabolic abnormalities. The site of insulin resistance in CKD is localized to skeletal muscle. Estimates based on fasting insulin concentration may not adequately capture insulin resistance in CKD because they largely reflect hepatic defects and because CKD impairs insulin catabolism. A variety of dynamic tests are available to directly measure insulin-mediated glucose uptake.

Summary—Insulin resistance may be an important therapeutic target in CKD. Complementary methods are available to assess insulin resistance, and each method has unique advantages, disadvantages, and levels of complexity. These characteristics, and the likelihood that CKD alters the performance of some insulin resistance measurements, must be considered when designing and interpreting clinical studies.

Keywords

chronic kidney disease; insulin resistance

Introduction

Chronic kidney disease (CKD) affects approximately 13% of the United States population [1]. It is associated with significant cardiovascular morbidity and mortality due to ischemic heart disease, stroke, peripheral artery disease, and sudden death [2,3]. The excess cardiovascular mortality in patients with CKD is not explained by traditional risk factors such as hypertension, smoking, hyperlipidemia, obesity, diabetes mellitus, or family history of coronary artery disease. Insulin resistance is increasingly recognized as a 'nontraditional' risk factor contributing to cardiovascular disease through endothelial dysfunction, oxidative

stress, dyslipidemia, systemic inflammation, and activation of the renin–angiotensin–aldosterone system [4]. Insulin resistance has been associated with increased risk of cardiovascular events and mortality in multiple large community-based cohort studies [5–9]. In addition, insulin resistance in dialysis patients has been linked to accelerated protein catabolism leading to protein energy wasting and malnutrition [10]. Insulin resistance is common in end-stage renal disease (ESRD), and possibly also in moderate-to-severe stages of CKD. Therefore, insulin resistance may be an important therapeutic target for reduction of cardiovascular mortality in patients with CKD.

Definition of insulin resistance

Insulin resistance is defined as reduced sensitivity of target organs to the biologic effects of insulin. Major functions of insulin include stimulation of glucose uptake by skeletal muscles, inhibition of hepatic glucose production, and inhibition of lipolysis in adipose tissues [11]. Insulin resistance is often distinguished as either hepatic insulin resistance or peripheral insulin resistance. Hepatic insulin resistance refers to impaired suppression of hepatic glucose production, whereas peripheral insulin resistance refers to impaired response to insulin in skeletal muscle and adipose tissue. Important causes of insulin resistance include genetic factors, obesity, physical inactivity, diet, medications, and aging. Other comorbid conditions that are strongly associated with insulin resistance are hypertension, diabetes, and hyperlipidemia (Fig. 1).

As insulin resistance develops, there is a compensatory increase in insulin release by pancreatic beta-cells to maintain circulating glucose in the normal range. As a result, there is a hyperbolic relationship between insulin sensitivity and pancreatic beta-cell function (Fig. 2) [11–13]. If pancreatic beta-cell function becomes insufficient, frank hyperglycemia ensues, leading to the development of type II diabetes.

Measurement of insulin resistance

There are multiple methods available to measure insulin resistance. The most widely used methods will be discussed in this review. These methods offer complementary approaches to studying glucose and insulin metabolism, and each method has unique advantages, disadvantages, and levels of complexity (Table 1) [14]. Moreover, different methods evaluate different aspects of glucose and insulin metabolism. In particular, it is important to distinguish tests assessing insulin resistance in the dynamic versus static state. Dynamic tests assess insulin sensitivity when the body is challenged with glucose or insulin. In this setting, glucose is primarily disposed of in skeletal muscle, and results largely reflect peripheral insulin resistance. Static tests assess insulin sensitivity in the fasting state, in which insulin sensitivity is largely determined by the ability of insulin to regulate hepatic glucose production, thereby reflecting primarily hepatic insulin resistance.

Dynamic methods of measuring insulin resistance

The gold standard for measuring insulin sensitivity is the hyperinsulinemic euglycemic clamp technique developed by DeFronzo *et al.* [15]. A continuous infusion of insulin is administered to increase the plasma insulin concentration to a high-physiologic range and a variable rate of exogenous glucose infusion is adjusted to maintain the plasma glucose concentration at a constant level. At steady state, the rate of exogenous glucose infusion equals the rate of glucose metabolized by the body. It provides a direct measure of whole-body sensitivity to insulin, primarily of skeletal muscle. At lower doses of insulin infusion, endogenous (hepatic) glucose production is not completely suppressed. In this setting, addition of labeled glucose can allow for specific assessment of the ability of insulin to suppress endogenous glucose production. This method can differentiate between peripheral

insulin resistance and hepatic insulin resistance. It provides a direct and precise measurement of insulin resistance.

Another commonly used method to measure insulin sensitivity is the frequently sampled intravenous glucose tolerance test (FSIVGTT) with minimal model analyses developed by Bergman *et al.* [16–18]. A bolus of glucose (typically 300 mg/kg) is administered intravenously and plasma glucose and insulin levels are measured frequently over 4 h. An infusion of insulin or tolbutamide to accelerate glucose disposal is given 20 min after the glucose bolus and improves parameter precision [18,19]. Changes in plasma glucose and insulin are fit using a modeling algorithm to derive indices. The insulin sensitivity index (ISI) is calculated as the rate of change in plasma glucose in response to prevailing insulin concentrations. As muscle and adipose tissues are the main organs involved in glucose disposal during this test, the ISI represents primarily peripheral insulin resistance [20].

The glucose clamp technique and the FSIVGTT are complex and labor intensive. A simpler method to measure insulin sensitivity is the oral glucose tolerance test (OGTT). In this test, 75 g of glucose is administered orally and multiple blood samples are obtained, usually at 0, 30, 60, 90, and 120 min. Insulin sensitivity is then calculated using various formulas. The following formulas have been validated against the glucose clamp technique. The first is the Matsuda index, denoted as $ISI = 10000 / \sqrt{(\text{Fasting glucose} \times \text{fasting insulin} \times \text{mean glucose} \times \text{mean insulin})}$ [21]. Another formula often utilized is the Stumvoll method [22], denoted as metabolic clearance rate (MCR) = $18.8 - (0.27 \times MBI) - (0.0052 \times \text{insulin}_{120}) - (0.27 \times \text{glucose}_{90})$, where insulin_{120} is the insulin concentration at 120 min and glucose_{90} is the glucose concentration at 90 min. One of the limitations of OGTT data is that the ISI derived is empirical because the rate of glucose appearance cannot be directly measured. In addition, the OGTT technically measures oral glucose tolerance, which reflects a combination of insulin resistance and the compensatory response of the pancreas. Therefore, while the formulae described above correlate well with insulin resistance, they may additionally reflect beta-cell function and substances that modulate beta-cell function, for example incretins.

Other less commonly used methods to assess insulin resistance include the insulin suppression test and the hyperglycemic clamp technique. In the insulin suppression test, a somatostatin or octreotide infusion is used to suppress endogenous insulin secretion. At the same time, insulin and glucose are infused for 3 h. Multiple blood samples are obtained during this time frame. The constant infusions of insulin and glucose will determine steady-state plasma insulin and glucose concentration. The steady state plasma glucose concentration is inversely related to insulin sensitivity. The insulin suppression test provides a direct measure of steady state plasma glucose in response to the ability of exogenous insulin to mediate glucose uptake [14]. In the hyperglycemic glucose clamp technique [15], a priming dose of glucose followed by variable rates of glucose infusion is administered to increase plasma to a prespecified hyperglycemic value as a 'square wave.' The hyperglycemic clamp is most often used to measure beta-cell function: insulin responses to hyperglycemia are evaluated as first phase (0–10 min), second phase (10–240 min), and total insulin response (0–240 min). Insulin resistance can be calculated by dividing the average glucose infusion rate by the average insulin concentration at steady state (180–240 min).

Static methods of measuring insulin sensitivity

Due to the complexity and time commitment of the dynamic methods, different approaches to estimate insulin sensitivity from fasting concentrations of glucose and insulin were developed. The most commonly used methods are the homeostasis model assessment of insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index

(QUICKI). HOMA-IR is calculated as: [fasting plasma insulin concentration (μ Units/ml) $\times$ fasting plasma glucose concentration (mmol/l)]/22.5 [23,24]. Higher values represent greater insulin resistance. QUICKI is calculated as $1/\log$ fasting plasma glucose (mg/dl) + $\log$ fasting plasma insulin (μ Units/ml) [25]. A number of other indices based on fasting insulin and glucose, with or without other clinical variables (e.g. triglyceride concentration, waist circumference, blood pressure), have also been developed.

The advantages of HOMA-IR and QUICKI are simplicity and the requirement for only fasting glucose and fasting insulin concentrations. However, these measurements are more variable compared to the euglycemic hyperinsulinemic clamp or the FSIVGTT due to a wide range of normal values for fasting plasma insulin [23,26,27]. Additionally, although strongly correlated with dynamic insulin sensitivity as compared to glucose clamp and FSIVGTT [28], fasting measures are more likely reflective of hepatic rather than muscle insulin sensitivity. More importantly for this review, these formulae have not been validated in the setting of CKD, as discussed below.

Insulin resistance in chronic kidney disease

Insulin resistance is a well known complication of ESRD. DeFronzo *et al.* [29] demonstrated that non-diabetic patients with ESRD are insulin-resistant using the gold standard hyperinsulinemic euglycemic clamp. Improvement in insulin resistance was observed with dialysis [29,30]. It is also probable that impaired tissue sensitivity may occur in early stages of CKD, regardless of the cause of renal disease. Fliser *et al.* [31] found that insulin resistance measured using the FSIVGTT is already present in early CKD, even when the glomerular filtration rate (GFR) is within the normal range. Interestingly, insulin resistance did not correlate with GFR among study participants with CKD in this study. Menon *et al.* [32**] recently found that inflammation and oxidative stress were evident early in patients with autosomal dominant polycystic kidney disease (ADPKD) even with preserved kidney function. However, this study found no difference in insulin resistance as measured by HOMA-IR between those with and without CKD. Other epidemiologic studies also suggest that insulin resistance is common in earlier stages of CKD [33,34]. Among National Health and Nutrition Examination Survey (NHANES) III participants without self-reported diabetes, lower estimated GFR was associated with higher mean fasting insulin concentrations and HOMA-IR scores [35]. Furthermore, among participants aged 70–79 years of the Health, Aging and Body Composition (Health ABC) study, kidney function was found to be independently associated with insulin resistance assessed by upper quartile of the homeostasis model assessment [36*].

The site of insulin resistance in CKD is localized to skeletal muscles [29]. Suppression of hepatic glucose metabolism remained normal in studies in which it was assessed [37]. A postreceptor defect has been recognized as the primary defect in CKD [38], although exact mechanisms remain to be elucidated. It is probable that an increased prevalence of known risk factors for insulin resistance, including obesity, sedentary lifestyle, and diet contribute to the excess insulin resistance observed in CKD [39]. In addition, there may be unique causes of insulin resistance in CKD [40]. These include various uremic toxins, metabolic acidosis, and vitamin D deficiency (Fig. 1). Asymmetric dimethyl arginine (ADMA) has been increasingly recognized as an important uremic toxin associated with CKD and insulin resistance. It is an endogenous inhibitor of nitric oxide production and is an important mediator of endothelial dysfunction [41]. ADMA is elevated in CKD and has been associated with increased homocysteine, obesity, increased carotid intima-media thickness, and left ventricular hypertrophy [42]. Metabolic acidosis may also play a significant role in insulin resistance in CKD. Chronic metabolic acidosis is associated with increased rates of protein catabolism and decreased protein synthesis through activation of the ubiquitin–

proteasome pathway, thereby contributing to chronic inflammation, impaired tissue growth and repair, and exacerbating the effects of insulin resistance [43]. Treatment with oral bicarbonate to maintain plasma bicarbonate levels above 22 mEq/l in children with ESRD undergoing dialysis improved insulin sensitivity measured by hyperinsulinemic euglycemic clamp [44]. Vitamin D deficiency is another factor that appears to contribute to insulin resistance in CKD [45]. Intravenous 1,25 vitamin D has been shown to stimulate insulin secretion and correct glucose intolerance in 1,25 vitamin D3-deficient animals following a glucose challenge [46]. A series of intervention studies showed that calcitriol administration significantly improved insulin sensitivity in ESRD patients undergoing hemodialysis [45,47–55].

Studies suggest variable pancreatic beta-cell function in response to insulin resistance in ESRD, resulting in glucose intolerance in some patients [40,56]. However, very little is known about the determinants of impaired beta-cell function in CKD or the adequacy of pancreatic beta-cell function in early stages of CKD.

Unique aspects of measuring insulin resistance in chronic kidney disease

The kidney plays a major role in the metabolism of insulin [57,58]. An estimated 30–80% of insulin in the systemic circulation is removed by the kidney [58,59]. Insulin has a molecular weight of 6000 daltons and is freely filtered by the kidney. Unfiltered insulin is also extracted from peritubular capillaries. Insulin is transported into the proximal tubules via carrier-mediated endocytosis and is metabolized into amino acids by the lysosomes [60]. Approximately 60% of total renal clearance of insulin occurs by glomerular filtration and 40% by extraction from the peritubular vessels.

As renal function is important in the handling of insulin, it is unclear whether high fasting insulin represents insulin resistance or decreased renal clearance in this population. As a result, the indices derived to estimate insulin resistance from fasting insulin and glucose concentrations in the general population, such as HOMA-IR and QUICKI, may not perform well in the setting of CKD. The euglycemic, FSIVGTT, insulin suppression test and hyperglycemic clamp are in theory not subject to bias by GFR because they directly measure glucose disposal in response to a standardized insulin challenge. OGTT-based measures of insulin have not been evaluated across a range of GFRs. Moreover, as insulin resistance in CKD is characterized by defects in skeletal muscle, these defects may not manifest in measurements based on fasting insulin, which largely reflect hepatic insulin resistance. Instead, dynamic tests may be needed to capture insulin resistance to insulin-mediated glucose uptake in skeletal muscle in the setting of decreased GFR.

Adipose tissue-derived circulating hormones, or adipokines, may offer new opportunity to assess insulin resistance in CKD and other disease states. Recently, HOMA-IR corrected by adiponectin and the leptin/adiponectin ratio (LAR) was shown to be highly correlated with the gold standard hyperinsulinemic euglycemic glucose clamp in African-American persons undergoing chronic hemodialysis [61**]. It should be noted that adipokines may reflect factors other than insulin resistance, such as adiposity and inflammation [62]. Further work is required to define the determinants of circulating adipokine concentrations in CKD and their utility as independent biomarkers of insulin resistance.

Though not a focus of this review, measurement of beta-cell function is further hampered in CKD by the fact that C-peptide is cleared by the kidney. Algorithms that account for changes in both insulin and C-peptide levels may need to be developed to accurately assess insulin secretion and beta-cell function.

Further research efforts are needed to establish validated methods to characterize the severity of insulin resistance in CKD, define the relationship between insulin resistance and GFR over its full range, understand pancreatic beta-cell compensation, and validate simple methods of measuring or estimating insulin resistance across a broad range of GFRs.

Conclusion

Insulin resistance may contribute to the development of cardiovascular disease and appears to be common in CKD. Insulin resistance may represent an important therapeutic target in this population. Multiple methods are available to measure insulin resistance. Each has advantages and disadvantages that need to be considered when designing and interpreting clinical studies. Further work is needed to refine the measurement of insulin resistance in CKD and to evaluate its causes, consequences, and treatment.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 682).

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Key points

- Insulin resistance is associated with significant morbidity and mortality.
- Unique metabolic factors contributing to insulin resistance in chronic kidney disease (CKD) include uremic toxins, metabolic acidosis, and vitamin D deficiency.
- Insulin may be an important therapeutic target in CKD.
- Multiple methods are available to measure insulin resistance, and each has advantages and disadvantages that need to be considered when designing and interpreting clinical studies.

Figure 1.
Mechanisms of insulin resistance in chronic kidney disease
CKD, chronic kidney disease.

Figure 2.
Relationship of beta-cell function and insulin sensitivity
Hyperbolic relation between B-cell function and insulin sensitivity, reproduced with permission from [11]. IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes.

Table 1

Summary of selected methods available to measure or estimate insulin resistance

Test	What is measured	Comments	Complexity/time
Hyperinsulinemic euglycemic clamp	Whole body uptake of glucose at steady state characterized by high normal circulating insulin concentration	Gold standard for measuring insulin resistance; insulin-mediated suppression of endogenous glucose production and lipolysis can be obtained with isotopes	++++/2–8 h
FSIVGTT with minimal model analyses	Modeled insulin sensitivity index primarily reflects peripheral insulin sensitivity; and simultaneously measures beta-cell function, e.g. acute insulin response to glucose	Cannot be combined with other techniques to assess intermediary metabolism	+++ /4 h
OGTT	Glucose and insulin response to a standardized oral glucose load; it primarily measures glucose tolerance, which reflects insulin resistance and beta-cell function in combination; insulin resistance calculated using validated formulae	Formulas can be used to estimate separate components of insulin resistance and beta-cell function (Matsuda index and Stumvoll index)	++/2–3 h
Insulin suppression test	The inverse of steady state plasma glucose is a measure of insulin sensitivity; measures the effects of exogenous insulin on glucose disappearance when endogenous insulin is suppressed	Direct measure of insulin sensitivity	+++ /3 h
Hyperglycemic clamp	Insulin resistance is calculated by the ratio of glucose uptake to insulin concentration at steady state	Gold standard for measuring beta-cell function	++++/3 h
HOMA-IR/QUICKI	Estimates insulin resistance from fasting glucose and insulin concentrations	Simple; reflects hepatic insulin resistance > peripheral insulin resistance	+

FSIVGTT, frequently sampled intravenous glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; OGTT, oral glucose tolerance test; QUICKI, quantitative insulin sensitivity check index.