

Insulin Resistance in CKD

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Insulin resistance is typically defined as decreased biologic action of insulin at its target organs (*e.g.*, liver, skeletal muscles) for any given blood concentration of insulin. Clinically it usually presents with hyperinsulinemia, glucose intolerance, hyperglycemia, and dyslipidemia. Insulin resistance can be physiologic (*e.g.*, in pregnancy) or pathologic. It may occur as a primary phenomenon contributing to the pathophysiology of type 2 diabetes or it may be secondary to other clinical disorders, and is often accompanied by cardiovascular sequelae (1,2). There are a number of well established direct and indirect methods for the quantification of insulin resistance that vary in complexity. The Minimal Model provides an indirect measurement of insulin resistance on the basis of a frequently sampled intravenous glucose tolerance test. With respect to practicability, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is simpler. The HOMA-IR derives an estimate of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations. Both methods have been intensively validated (3). Since the development of the hyperinsulinemic euglycemic clamp technique by DeFronzo *et al.* in 1979, impaired insulin-mediated glucose uptake to the skeletal muscles (a major target organ) could be directly quantified. It requires a high insulin blood level maintained by continuous infusion of insulin in order to suppress hepatic gluconeogenesis, followed by glucose infusion in order to preserve euglycemia (4). The advantage of this time- and resource-consuming technique, compared with the above methods, is that it can be used to measure tissue-specific insulin action and glucose uptake in skeletal muscles (3). The euglycemic clamp has since been the gold standard for pharmacodynamic studies in diabetes drug development and diagnostic evaluation, and has been very useful for intensive physiologic studies. The much simpler HOMA-IR is more appropriate for large epidemiologic studies when evaluation of insulin sensitivity is of secondary interest (1). The results of HOMA-IR and Minimal Model analysis have shown reasonable correlation with the reference hyperinsulinemic euglycemic clamp method in several studies of distinct populations, but the correlation is notably weaker in insulin-resistant populations (5,6). Thus, caution should be exercised when making comparisons between studies due to variations in the infusion protocols, sampling, and assay methods.

By using the gold standard euglycemic clamp technique, an inadequate target cell response to the actions of insulin in patients with CKD was recognized decades ago (7). Since then, past and recent studies have revealed that insulin resistance occurs in patients with CKD at different stages of kidney impairment (8–11). It was actually shown in a CKD population comprising patients with autosomal dominant polycystic kidney disease and IgA-GN that a syndrome of insulin resistance is already present in the earliest stages of kidney disease (*i.e.*, even before the true GFR determined by inulin clearance is decreased). No difference in insulin resistance was observed between patients with autosomal dominant polycystic kidney disease and IgA-GN, suggesting that the impairment of kidney function itself, rather than the etiology of a specific kidney disease, causes insulin resistance (12). Furthermore, the finding of insulin resistance in patients with CKD even before detection of reduced GFR renders uremia and secondary complications of CKD, such as anemia, hyperparathyroidism, vitamin D insufficiency, or metabolic acidosis, unlikely as the underlying mechanisms of insulin resistance. However, the causal nature of this relationship remains poorly defined.

A growing body of evidence reveals that the kidney is an important organ of glucose homeostasis. Turnover studies using radiolabeled glucose have demonstrated that renal glucose production and utilization are relevant components of glucose metabolism in humans (13). Thus, it is hypothesized that kidney dysfunction would lead to complex disturbances of glucose appearance in the circulation, resulting in insulin resistance. Metabolic studies in patients with type 2 diabetes mellitus have revealed that renal gluconeogenesis—similarly to hepatic gluconeogenesis—is not suppressed by insulin to a similar extent as in healthy individuals (14). This observation points to the presence of insulin resistance on the level of renal glucose metabolism. Such information is not available for patients with kidney dysfunction, and further experimental and clinical studies are warranted to elucidate the action of insulin in patients with CKD. Another factor that might be involved in derangements of glucose metabolism in patients with CKD is abnormal peripheral glucose disposal due to modified skeletal muscle composition. Friedman *et al.* discovered that the increase in insulin-stimulated glucose transport was significantly diminished in isolated muscle fibers of uremic patients supposedly by

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affecting postreceptor signaling pathways (15). A new mechanism of impaired insulin signaling in the muscle by inflammation-triggered overexpression of the signal regulatory protein α in the muscle of patients with CKD was recently reported (16). A plethora of inflammatory pathways are thought to be involved in the development of insulin resistance mediated by the activity of proinflammatory cytokines and adipokines, but experimental results are conflicting. In particular, the adipokine adiponectin demonstrated its ability as a significant inverse predictor of fatal and nonfatal cardiovascular events among patients with CKD (9,17,18).

Per se, the finding of insulin resistance in patients with CKD would not be clinically remarkable if we would not ask whether insulin resistance influences the prognosis of affected individuals. In an attempt to prove its clinical relevance, a study by Shinohara *et al.* has renewed the interest in insulin resistance because the results showed that insulin resistance assessed by HOMA-IR is an independent predictor for cardiovascular mortality in nondiabetic patients with end stage CKD (8). Although there is growing evidence for such an association in advanced kidney failure, the link between insulin resistance and cardiovascular mortality is less intensively studied in early CKD. The study by Xu *et al.* in this issue of *CJASN* (19) is the first to address the important question of whether insulin resistance is an independent predictor of cardiovascular mortality in a population with mild-to-moderate kidney impairment by using the sophisticated euglycemic clamp technique. The study included 446 nondiabetic men aged 70–71 years from the Uppsala Longitudinal Study of Adult Men cohort. The inclusion criterion for analysis was an eGFR of 20–60 ml/min per 1.73 m² calculated on the basis of serum cystatin C concentrations. Exclusion criteria were incomplete data and preexisting diabetes (19). Definite strengths of the study were the use of serum cystatin C to estimate GFR in an elderly population and the assessment of insulin resistance by the euglycemic clamp technique. With respect to the former, GFR in elderly individuals is known to be physiologically reduced, but studies have shown that cystatin C is a reliable marker of even subtle GFR changes in elderly individuals and is diagnostically superior to serum creatinine (20). Among the studied population, only 12.5% of patients were identified as insulin sensitive. As many as 63.5% of patients were detected to be at least insulin intolerant and 24% were insulin resistant according to the glucose infusion rate required to maintain euglycemia in response to the amount of insulin infused. The data of Xu *et al.* support the finding that insulin resistance can already be observed in early CKD stages. Insulin resistance was not directly associated with significantly increased cardiovascular mortality in patients with stages 3–4 CKD, but graded relations among physical inactivity and smoking, together with insulin resistance, were identified as a deleterious combination for increased mortality (19). Interestingly, in line with other observations, the presence of insulin resistance was independent of overweight—a major risk factor in the classic metabolic syndrome (8,9). However, because of the moderate number of events during follow-up and the highly selected cohort, no final conclusion about the association of insulin resistance with cardiovascular mortality should be drawn from this study concerning the general CKD

population. de Boer *et al.* recently reported similar findings about insulin resistance and mortality in a comparable population (21). Becker *et al.* found a significant association of insulin resistance with cardiovascular events in a cohort study of 227 nondiabetic patients with mild and moderate CKD during a 7-year follow-up (9), and Shinohara *et al.* had similar findings in an investigation of a population of patients with ESRD (8). The latter studies were conducted in younger populations and assessed insulin sensitivity with the HOMA-IR (8,9). The use of different methods for quantification of insulin sensitivity may at least partly explain the conflicting results, and further experimental and clinical research efforts are therefore needed in order to clarify the prognostic implications of insulin resistance in CKD.

Nevertheless, addressing this issue is of major interest because cardiovascular complications are a significant cause of mortality in patients with CKD. This excess cardiovascular risk is also evident in patients with CKD not yet on dialysis. Identifying independent cardiovascular risk factors in the CKD population should allow us to begin the process of modifying unhealthy lifestyles, such as smoking and physical inactivity, or target them in intervention studies (22). Finally, the aim of this line of reasoning and future research is to apply an intervention grounded on physiologic evidence that can modify cardiovascular disease in CKD, improving the prognosis in our patients.

Disclosures

None.

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See related article, “Clinical Correlates of Insulin Sensitivity and Its Association with Mortality among Men with CKD Stages 3 and 4,” on pages 690–697.