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Effect of Insulin Resistance in Chronic Kidney Disease

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Abstract

Insulin resistance accompanies many well-established cardiovascular risk factors, such as obesity, hypertension, dyslipidaemia and type 2 diabetes. Since cardiovascular disease (CVD) is the leading cause of death in patients with end stage renal disease (ESRD), insulin resistance is thought to play a role in the morbidity and mortality associated with ESRD. This paper reviews the available information on insulin resistance in patients with impaired kidney function as well as those on renal replacement therapy in the form of maintenance hemodialysis. Potential mechanisms for the dynamic changes in insulin resistance, which occur through the different stages of kidney disease, are also discussed. We hypothesize that stabilizing insulin sensitivity may have a positive effect on improving outcome in ESRD subjects.

Keywords: Chronic kidney disease, Obesity

Introduction

The obesity pandemic of recent decades is a major contributor to the increased incidence of insulin resistance and the metabolic syndrome, which have led to an increase in type 2 diabetes [1-6] and its complications. Both obesity and type 2 diabetes can lead to chronic kidney disease (CKD) and ultimately ESRD [6-9]. The prevalence of ESRD is rapidly increasing; a fact that can be contributed to the obesity pandemic and its metabolic complications, as well as the longer lifespan and the improved survival of these patients, which means more subjects develop long-term complications of disease. CKD is a growing public health problem that is important not only because of its own burden, but because it is also recognized as an independent risk factor for cardiovascular disease (CVD); even early stage CKD causes an estimated 40-100% increase in risk of cardiovascular events [10]. The effect of prevention, stabilisation or reversal of CKD is therefore a subject that warrants further insight that can only be gained through research aimed at this specific at-risk population. However, despite the huge body of published evidence on the subject, it seems that our understanding of the metabolic status of these patients is still extremely limited, a factor that may be attributed to the quantity of metabolic abnormalities identified in these complex individuals.

When trying to single out a common denominator for conditions leading to morbidity and mortality in renally impaired subjects, insulin resistance is a topic that merits closer attention. Insulin is a hormone secreted by the pancreatic beta cells and has many effects including: influencing amino acid uptake, protein synthesis, proteolysis, lipolysis, triglyceride secretion, glucose uptake, glycogen synthesis and gluconeogenesis. For these effects to be regulated by insulin, however, sensitivity to the insulin hormone is as crucial as its presence. Failure of the beta cells to secret the insulin molecule results in type 1 diabetes, while the resistance of peripheral tissue designed to implement insulin's effects results in 'insulin resistance' and ultimately type 2 diabetes. The failure of insulin's target cells, namely hepatocytes, myocytes and adipocytes, to response to normal concentrations of the hormone leads to a need for greater stimulation that is achieved through increased production by the beta cells. Once individuals become insulin resistant, normoglycaemia is initially achieved by modest increases in beta-cell mass and/or an increase in insulin secretion [11] and for euglycaemia to be maintained hyperinsulinaemia needs to be sustained. The presence of insulin resistance in uraemic subjects was first identified in 1978 and shown to exist in non-diabetic uraemic subjects [12]. Factors affecting insulin production, half-life, transportation, degradation and the insulin receptor can all lead to imbalances that may result in changes in insulin sensitivity. Here, we discuss some of these factors in the CKD patients.

Insulin resistance and inflammation

It is widely believed that insulin resistance may be a consequence of inflammation [13]. Using C-reactive protein (CRP) measurements as a marker of inflammation, current evidence shows elevated levels in 30-50% of predialysis, haemodialysis and peritoneal dialysis patients, indicating an inflammatory state [14-18]. As the condition is also present in predialysis patients, the inflammatory response is probably aided by factors not related to the dialysis process, such as residual renal function, ethnicity, gender and age [19-21]. Loss of renal function has been shown to be associated with elevated serum cytokine levels [19] and creatinine clearance has a positive correlation with a number of cytokines, including IL-1, IL-6 and TNF-alpha, and their soluble receptors in the predialysis population [22-26]. That said, the presence of the inflammatory state is primarily found in patients undergoing the dialysis procedure [27-29]. In addition to the factors mentioned above, the inflammatory response in the dialysed population is enhanced by dialysis-specific factors such as non-biocompatible membranes, non-sterile dialysates and the back-leak of dialysate across the dialysis membrane [30-34]. In non-diabetic ESRD patients, the increase in insulin resistance could therefore be attributed to the presence of an inflammatory state induced by uraemia.

It was first shown in 1993 that TNF-alpha, a pro-inflammatory cytokine produced by adipose tissue and over-produced in obesity, was able to induce insulin resistance [35,36]. Within a few years, the concept of adipose tissue as a site for cytokine production was well-established, and the list included leptin, IL-6, resistin, and adiponectin [37-41]. While the latter is recognised as an anti-inflammatory molecule, all other adipokines possess pro-inflammatory qualities. It has been shown that the pro-inflammatory adipokines also induce insulin resistance [42-44], while the anti-inflammatory adiponectin is identified as an 'insulin-sensitizing agent' [45,46]; whether these effects are a cause or consequence of the inflammatory effects is still debated, though. Studies in insulin-resistant groups other than those with diabetes, i.e. individuals with obesity and hypertension, have lent further support to the adverse effect of TNF-alpha in the development of insulin resistance [44,47]. The important clinical issue is that the concurrent presence of insulin resistance and the inflammatory state has a detrimental effect on the cardiovascular system, as inflammation is a key feature of both atherosclerosis and CVD [13].

Insulin resistance and CVD

Insulin resistance is associated with multiple risk factors for atherosclerosis and CVD, including hypertension, dyslipidaemia and glucose intolerance and/or type 2 diabetes. Several studies have shown hyperinsulinaemia and other indices of insulin resistance to be associated with prevalent atherosclerosis and heart disease [48-52], incident congestive heart disease (CHD) [48], incident stroke [49], and risk of death from CHD [50-53]. Patients with ESRD are known to be insulin resistant and have multiple cardiovascular risk factors, advanced atherosclerosis and an increased risk of cardiovascular mortality. Current literature suggests that a quantified value of insulin resistance, such as the homeostatic model assessment index of insulin resistance or HOMA-IR is an independent predictor of cardiovascular disease in patients with type 2 diabetes [53] as well as in individuals without diabetes [54, 55]; the latter is also true in the ESRD population [1].

Insulin resistance is important in that it is associated with the clustering of CVD risk factors such as hypertension, dyslipidaemia and glucose intolerance, which synergistically increases the risk of atherosclerosis [56]. It is therefore expected that the effect of insulin resistance on CV mortality is dependent on these factors, as it is the underlying mechanism for their coexistence. However, insulin resistance has also been identified as an independent risk factor for CVD in ESRD patients without diabetes [1]. Interestingly, the effect of insulin resistance on CV outcome is independent of CRP levels. As this effect is also independent of BMI, and BMI seems to be negatively associated with CVD and mortality in the ESRD population [57], it is possible that insulin resistance and adiposity per se have different roles in CV mortality in the ESRD population.

Takenada et al. looked at HOMA-IR values and their relationship with cardiovascular events in 81 patients [58] and showed that MHD subjects have higher HOMA-IR values than the reference range, and that higher HOMA-IR was associated with higher rate of cardiovascular events [59]. Unfortunately, we have not been able to find any large prospective study looking at HOMA-IR values and how they change with progression of renal failure in patients with and without diabetes, and how this change may affect morbidity and mortality. As HOMA-IR is a fairly practical and inexpensive method of measuring insulin resistance, and as there is evidence of contribution of insulin resistance to cardiovascular disease, it has been recommended that a routine HOMA-IR screening in CKD and MHD subjects may help in recognising subjects most at risk of progressive vascular disease and in need of greater risk factor modification [59].

Insulin resistance and CKD

The kidney and the liver are the main sites for insulin clearance, with the kidney removing 50% of peripheral insulin by glomerular filtration [60] and the liver removing approximately 50% during the first portal passage [61,62]. In addition to glomerular filtration, proximal tubular reabsorption and degradation is responsible for disposal of insulin in the kidney [63]; in fact, more than 99% of the filtered insulin is reabsorbed in the proximal tubule and very little insulin is actually excreted in urine [64], which is why the renal clearance of insulin is considerably greater than the GFR. Peritubular insulin uptake increases as renal function deteriorates, and insulin clearance is maintained until the GFR reaches 15-20 ml/min. From this point on, insulin clearance falls rapidly [65]. Therefore, insulin resistance accompanied by hyperinsulinaemia, glucose intolerance and dyslipidaemia, is one of the characteristics of the uraemic state.

As well as decreased clearance, insulin's half-life is increased in uraemia, mainly due to impaired degradation in non-renal tissues; the accumulation of uraemic toxins is thought to cause an inhibition of the insulin degradation system, especially by the liver, which is responsible for clearing about 50% of the insulin secreted into the portal system [65]. Hepatic insulin uptake is receptor mediated and therefore persistence of raised circulating insulin leads to its down regulation and further decrease in clearance. Other causes of insulin resistance in ESRD include physical inactivity [11], and the accumulation of adipokines in uraemic plasma. As explained above, insulin resistance may be induced by pro-inflammatory cytokines such as TNF-alpha, IL-6 and leptin. The accumulation of these molecules may be responsible for the presence of insulin resistance, especially in non-obese ESRD patients.

Using techniques such as the euglycaemic hyperinsulinamic clamp has allowed researchers to document diminished insulin-stimulated glucose uptake by extrahepatic tissue in patients with renal failure [66,67]. Although insulin sensitivity seems to be reduced early on in the natural history of CKD, in fact when GFR is still within the normal range, it is not problematic in most patients as the pancreatic beta-cells continue to secrete enough insulin to overcome this state, thus leading to hyperinsulinaemia [68]. But at the extreme end of the spectrum, in the more severely ill patients with profound renal failure, anaemia, acidosis and hyperparathyroidism, the beta-cells fail to secrete enough insulin to keep up with the reduced insulin sensitivity, which leads to impaired glucose tolerance and hyperglycaemia [69-71].

There are metabolic consequences of renal failure that have been shown to effect insulin sensitivity, including metabolic acidosis, hyperparathyroidism, anaemia and malnutrition. Correction of metabolic acidosis in CKD subjects improves insulin sensitivity [72], and although exact mechanisms are not clear, it is thought that metabolic acidosis may contribute to vitamin D deficiency in uraemia [73], which has been repeatedly shown to contribute to insulin resistance [74-77]. The secondary hyperparathyroidism present in renal failure also affects insulin sensitivity through vitamin D levels; vitamin D increases beta cell capacity for biosynthesis and therefore increases insulin secretion, as well as accelerates the conversion of proinsulin to insulin [78]. Administration of vitamin D has been shown to improve insulin sensitivity in type 2 diabetic subjects [79], non-diabetic subjects [80], as well as dialysis patients [69,81]. Current

literature suggests that the increased intracellular calcium concentration due to increased PTH may also be a contributing factor for insulin secretion impairment in CKD [81,82]; however, although parathyroidectomy in patients with hyperparathyroidism does not seem to ameliorate insulin resistance [83-88], it has been shown to improve insulin secretion [88,89]. Correction of anaemia has also been shown to reverse insulin resistance and hyperinsulinaemia in haemodialysed subjects [90], although more indirect mechanisms are likely to be involved, for example better exercise tolerance after treatment which leads to increased mobility.

The presence of insulin resistance in the early stages of CKD suggests that insulin resistance may be a driver, rather than a consequence, of CKD, even in non-diabetic subject. Chen et al. have shown a strong, positive, significant, and dose-response relationship between insulin resistance, insulin level and risk of CKD among non-diabetic subjects [91]. Other studies, mostly prospective, have shown that the presence of diabetes is associated with an increased risk of ESRD of both diabetic and non-diabetic origin [59,68,92].

Although data on the relationship between insulin resistance and non-diabetic CKD is sparse, several small studies have shown the presence of insulin resistance in non-diabetic CKD patients [68,93,94], and one prospective study has shown that insulin resistance appears earlier than microalbuminuria in non-diabetic subjects [95]. These findings suggest that early detection and correction of insulin resistance may benefit patients in delaying the onset of CKD, even in non-diabetic patients.

Kobayashi et al. measured insulin sensitivity by use of the euglycaemic clamp method in 10 HD and 9 CAPD subjects before and 5 weeks into dialysis and showed that it improves significantly with both modalities of dialysis, and is comparable to the insulin sensitivity levels of their healthy controls [96]. Other small-scale studies have also shown insulin sensitivity to improve on dialysis [97-99]; this suggests that while loss of kidney function causes insulin resistance, haemodialysis corrects the situation, and subjects' insulin sensitivity returns to near normal levels.

Reduced clearance, increased half-life and impaired secretion of insulin are the main aspects of insulin resistance in CKD; depending on the severity of the subjects' condition and comorbidities, one or all of these factors may contribute to establishing varying degrees of insulin resistance and its cardiovascular manifestations.

Conclusion

In summary, insulin resistance is a known predictor of cardiovascular events and cardiovascular death in the general population [48,100-103]. It is also the common link between obesity, hypertension, dyslipidemia and diabetes, and therefore it is important to understand its behavior in ESRD. Patients with chronic kidney disease develop insulin resistance, and this is due to loss of kidney function [93,94], increased levels of insulin resistance inducing adipokines such as TNF-alpha and leptin [104-106], reduced secretion due to increased intracellular calcium (caused by PTH imbalance) [70,71], and physical inactivity [11]. It has also been shown that insulin resistance can be a contributing factor to CKD, even in non-diabetic subjects [91,95]. Insulin resistance is improved in the hemodialysis population, but the exact mechanisms for this improvement are yet unknown. It is important to note, however, that while the CKD population may be categorized as insulin-resistant while the haemodialysed population is categorized as less-insulin-resistant, individuals within each group may exhibit completely different characteristics. The amount of insulin resistance lies in the balance of different metabolic pathways that enhance insulin resistance and those that negate it. In the haemodialysed population, the hemodialysis process itself is the negating factor. Reduced clearance of insulin and its prolonged half-life in the CKD population have been reported to lead to reduced insulin requirements and increased hypoglycemic episodes [107-109].

Given that insulin resistance may be an important factor in relation to outcome in the ESRD population, it is imperative that each patient is assessed as an individual in order to ascertain their insulin sensitivity status. Further research should be targeted at elucidating the mechanisms involved in the natural history of insulin resistance through the spectrum of CKD.

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