Carbohydrate Metabolism in Chronic Kidney Disease

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Abstract

Insulin resistance (IR) is a common feature of chronic kidney disease (CKD), but the exact underlying mechanism is still an enigma. Studies have shown that IR and the associated altered metabolic milieu, even in the absence of Diabetes is an important contributory factor to the development of cardiovascular disease in CKD. There is growing evidence that modification of intestinal flora and activation of immune-inflammatory pathways which have been implicated in the pathogenesis of IR in obese and diabetic patients. All these pathways ultimately lead to ectopic lipid accumulation with impaired insulin signalling. Indeed, recent studies show impaired intestinal barrier function and altered gut microbiome in non-diabetic patients with CKD that can contribute to the prevailing inflammation, and the production and absorption of toxins generated from bacterial metabolism. The specific role of individual uremic toxins in the pathogenesis of IR has been highlighted in rodents. Moreover, correcting some uraemia-associated factors by modulating the intestinal flora improve insulin sensitivity.

Keywords: Carbohydrate metabolism; Glucose metabolism; Insulin resistance; Chronic kidney disease

Abbreviations :CKD: Chronic Kidney Disease; IR: Insulin Resistance; IRS: Insulin Receptor Substrate; URMs: Uraemia Retention Molecules; GFR: Glomerular Filtration Rate; PTH: Parathyroid Hormone; ATP: Adenosine Triphosphate; HGP: Hepatic Glucose Production: WAT: White Adipose Tissue; PKC: Protein Kinases C; HD: Hemodialysis; VLDL: Very Low Density Lipoprotein; eGFR: estimated Glomerular Filtration Rate; JNK: Jun N-Terminal Kinase; TLR: Toll-Like Receptor; MAPKs: Mitogen-Activated Protein Kinases; NF-kB: Nuclear Factor-kB; mTOR: Mammalian Target of Rapamycin

Introduction

CKD is typically associated with several disturbances in carbohydrate handling may be present with tissue insulin insensitivity being primarily important. Insulin Resistance (IR) is very common in CKD [1]. While alterations in insulin degradation and insulin secretion may contribute [2-4]. Individual differences explain the variable plasma levels of insulin and glucose seen in fasting and following a glucose challenge. Some patients have hyperglycemia while others maintain normoglycemia by raising plasma insulin levels.

Chronic kidney disease (CKD) is a risk factor for cardiovascular disease, and this increase in disease burden cannot be solely explained by traditional cardiovascular risk factors [5]. Studies have shown that IR and the associated altered metabolic milieu, even in the absence of Diabetes is an important contributory factor to the development of cardiovascular disease in CKD [5]. In this review, we will discuss the changes in carbohydrate metabolism that occur in chronic kidney disease (CKD) and its implication in non-diabetics.

Discussion

In the 1980s, DeFronzo et al. [6], using the 'gold standard' euglycemic hyperinsulinemic clamp technique, found evidence of insulin resistance (IR) in CKD patients [6]. They suggested that the site of IR lies in the binding of insulin to its receptor and can be reversed by dialysis. It is now well established that the decline of renal function is associated with the development of IR with impaired insulin-induced glucose utilization of peripheral target tissues. Since this seminal study, there has been a renewed interest in IR in CKD, especially as IR is an independent risk factor for cardiovascular morbidity and mortality in patients with CKD [7]. Although the underlying causes of IR in CKD remain unclear, understanding the mechanisms is pivotal. In obesity and diabetes, emerging studies suggest an interconnected network linking innate immunity and inflammation to metabolic diseases, and the major role of adipose tissue and intestinal flora in the control of energy metabolism and insulin sensitivity [8]. There is strong evidence that there is an increased colonic generation or absorption of bacterial URMs in CKD [9,10]. All these pathways are closely linked to changes in fatty acid uptake, lipogenesis and energy metabolism, which can lead to ectopic lipid accumulation in visceral tissues and impair insulin signalling through inhibitory serine phosphorylation of insulin receptor substrate (IRS) [8-10].

During the last two decades, several cellular and animal models have enabled us to better understand the cellular and molecular mechanisms underlying IR in CKD. This has rapidly

progressed with the availability of tools such as high-resolution mass spectrometry, 16S rRNA gene sequencing, metabolomics and metagenomic sequencing enabling even broader insights into the composition of uraemia retention molecules (URMs) and gut microbiota.

Normal renal handling of Insulin

The kidney plays a central role in the metabolism of insulin in normal subjects [2,3,11]. Having a molecular weight of 6000, Insulin is freely filtered. Glomerular filtration accounts for approximately 60% of the total renal insulin clearance. The rest 40 percent is extracted by the peritubular vessels by carrier-mediated endocytosis and subsequently metabolized to amino acids by lysosomal enzymes [6]. The net effect is that the final urine has <1 percent of filtered insulin.

The renal clearance of insulin is 200mL/min, significantly exceeds the normal glomerular filtration rate (GFR) of 120mL/min due to the contribution of tubular secretion. From this rate of renal clearance, it can be calculated that 6 to 8 units of insulin are degraded by the kidney each day, which accounts for approximately 25 percent of the daily production of insulin by the pancreas. The contribution of renal metabolism is enhanced in diabetic subjects receiving exogenous insulin since injected insulin enters the systemic circulation directly, without first passing through the liver [12].

Insulin degradation

There is little change in the metabolic clearance rate of insulin in renal disease until there has been a substantial reduction in the glomerular filtration rate (GFR) [2]. Increased peritubular insulin uptake is able to compensate for reduced filtration until the GFR has fallen to less than 15 to 20mL/min [13]. At this point, there is a dramatic reduction in insulin clearance that is also mediated by a concomitant decline in hepatic insulin metabolism [2]. The hepatic defect may be induced by a uremic toxin since it is largely reversed with adequate dialysis [14]. These findings become important clinically in diabetic patients treated with insulin.

Insulin secretion

Blunted insulin secretion in the face of ongoing insulin resistance in some patients with CKD tend to have the greatest impairment in glucose tolerance. One factor that can suppress insulin release in chronic kidney disease (CKD) is the associated metabolic acidosis [3].

In addition, excess parathyroid hormone (PTH) may interfere with the ability of the beta cells to augment insulin secretion in response to hyperglycemia or amino acids [15-17]. A PTH-induced elevation in the intracellular calcium concentration may be responsible for the impairment in insulin release by decreasing both the cellular content of adenosine triphosphate (ATP) and Na-K-ATPase pump activity in the pancreatic beta cells [18]. In experimental animals, these changes can be prevented by prior parathyroidectomy or by the administration

of the calcium channel blocker verapamil [16,17]. The common deficiency of calcitriol (1,25-dihydroxyvitamin D) in CKD also may contribute to the impairment in insulin secretion. As an example, acute administration of calcitriol to hemodialysis patients has been shown to enhance insulin release and improve glucose tolerance [19]. This effect was independent of changes in the plasma concentrations of calcium or PTH [20].

As with the tissue sensitivity to insulin, hemodialysis has been shown to improve the insulin secretory response to glucose [14]. The mechanism by which this occurs has yet to be determined, but partial correction of the acidemia may contribute.

Studies evaluating the effect of erythropoietin on insulin and carbohydrate metabolism in CKD have produced conflicting results. A study showed that erythropoietin administration was associated with increased insulin secretion and decreased blood glucose levels following a test meal [21] while no change was shown in another [22].

Insulin Resistance (IR)

IR is characterized by resistance to the effects of insulin on glucose uptake, metabolism or storage and is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output. These functional defects may result from impaired insulin signalling in the target organs, which may be linked to reduced insulin binding to its receptor, blunted receptor phosphorylation, decreased tyrosine kinase activity and/or impaired phosphorylation of IRS proteins. A major mechanism by which insulin signalling can be negatively regulated is via phosphorylation of certain serine residues on IRS-1/2 [1,23,24].

Impaired tissue sensitivity to insulin is almost universal in all patients with CKD [2-4] and even in patients with only mild to moderate reductions in renal function [11,25]. Plausible mechanisms which account for the reduced insulin-mediated glucose handling include:

1. Increased hepatic gluconeogenesis not suppressible with insulin;

2. Reduced hepatic and/or skeletal muscle glucose uptake; and

3. Impaired intracellular glucose metabolism due either to decreased glucose oxidation or to diminished glycogen synthesis.

Both experimental and clinical studies suggest that hepatic glucose uptake and production are normal in CKD and that the primary site of insulin resistance is the skeletal muscle [2,3]. The putative primary mechanism is a post receptor defect [26,27]. Furthermore, the abnormality appears to specifically involve glycogen synthesis as the rate of glucose oxidation is normal [27]. Quite interestingly other actions of insulin, such as cellular uptake of potassium and inhibition of proteolysis, are maintained in renal failure [27-29].

CKD patients demonstrate a normal or mildly elevated glucose level during fasting and an enhanced increase of glucose following glucose loading. Patients may develop hyperglycaemia or maintain normoglycemia at the expense of hyperinsulinemia [1], suggesting peripheral resistance to the action of insulin. These changes are often masked by a decline in the metabolic clearance of insulin that occurs as the glomerular filtration rate drops <15-20mL/min [30].

As muscle tissue is the primary site for glucose disposal [31,32] altered insulin sensitivity is considered to affect primarily muscle rather than liver. Friedman et al. [33] demonstrated that the increase in insulin-stimulated glucose transport was significantly reduced by 50% in muscles from uremic patients without reduced glycogen synthase activity [34]. However, the increase in hepatic glucose production (HGP) during uraemia is a subject of controversy. Currently, there is no data on the effect of uraemia on adipose tissue insulin sensitivity in human.

Several studies have investigated the cellular mechanisms of IR in CKD. In partially purified insulin receptors prepared from human or rat [35] skeletal muscle, receptor number, insulin binding, β-subunit receptor auto-phosphorylation and tyrosine kinase activity were all unchanged in CKD, suggesting that the IR observed in uremic patients is due to a post-receptor defect of insulin pathway [35,36]. One or several unknown circulating molecules unique to uraemia could induce IR and downstream dysfunction of the IRS-PI3K-Akt pathway. However, numerous fractionation studies, which attempted to decipher the precise molecular nature of this factor, have so far not been conclusive. The components present in the uremic serum and involved in IR in CKD are multiple, resulting from pathophysiological alterations related to CKD (acidosis, disturbed bone metabolism, accumulation of URMs, post-translational protein modification) and non-specific factors (dyslipidemia, systemic inflammation, oxidative stress, etc.) [1,23,24].

Acidosis & IR

The concept that metabolic acidosis might be the cause of IR in CKD stems from both animal and human studies with ammonium chloride load induces IR. Finally, in human the degree of acidosis has been shown to correlate positively with the IR in CKD subjects [37].

Vitamin D deficiency, hyperparathyroidism & IR

There is evidence that the vitamin D and/or parathyroid hormone (PTH) axis is important in the pathogenesis of IR during uraemia. Several mechanisms have been proposed, including gene polymorphisms and the immunoregulatory function of vitamin D and inflammation. Vitamin D may have a beneficial effect on insulin action by stimulating the expression of insulin receptors enhancing insulin responsiveness for glucose transport [38]. After 4 weeks of intravenous 1,25-(OH)2 vitamin D3 therapy, IR is corrected in hemodialysis (HD) patients, in the absence of PTH suppression [39]. In addition to the classical actions of PTH on calcium metabolism, experimental data show that PTH plays a role in insulin sensitivity. PTH treatment of differentiated adipocytes suppresses insulin-stimulated glucose uptake and insulin signalling via cAMP pathway, potentially through the serine phosphorylation of IRS-1 [40]. PTH also stimulates HGP from lactate and pyruvate [41]. Finally, correction of secondary hyperparathyroidism in patients with CKD improves the glucose intolerance and insulin secretion [41].

Protein carbamoylation & IR

Carbamylated proteins (non-specific binding reaction between cyanic acid (CHNO) formed from urea and protein) are increased with decreased renal function and associated with the alteration of metabolic pathways [42].

URMS (Uremic toxins) & IR

The uremic syndrome is attributed to the progressive retention of numerous compounds, which, in healthy individuals, are normally excreted or metabolized by the kidneys. These URMs can originate from endogenous metabolism, microbial metabolism or exogenous intake. Growing evidence suggests that the accumulation of these compounds is an important mechanism of a specific state of IR in uraemia, although at present human studies are lacking.

Tissue oxygen delivery & IR

• The degree of tissue insensitivity to insulin directly correlates with maximal aerobic work capacity, indicating that physical training may ameliorate insulin resistance in patients with renal failure. It was shown in a study with long-term exercise training in patients on maintenance hemodialysis [43].

• Anaemia may also be an important factor underlying insulin resistance in uremia as evidenced by an approximate 50 percent increase in insulin-induced glucose utilization following correction of anemia with erythropoietin [44,45].

White adipose tissue & IR

White adipose tissue (WAT) dysfunction is now considered to be an important source of molecules that are responsible, at least in part, for the metabolic disturbances in these patients [46]. Several works over the last two decades have led to a unifying hypothesis that intracellular accumulation of toxic lipids species termed 'lipotoxicity' triggers activation of novel protein kinases C (PKC) with subsequent impairments in insulin signalling via inhibitory serine phosphorylation of IRS-1 [47]. Adipose tissue–derived proinflammatory cytokines such as TNF-α could actually cause IR in experimental models provided the first credible hypothesis linking inflammation to the development of IR [47].

Chronic inflammation & IR

Research in the last decade has shown chronic low-grade inflammation has an important role in the molecular mechanism of insulin resistance in CKD. This is one of the postulated mechanisms of vascular disease [48-50].

Gut microbiata & IR

During the last two decades, several cellular and animal models have enabled us to better understand the mechanisms underlying IR in CKD. The field has progressed rapidly with the availability of tools such as high-resolution mass spectrometry, 16S rRNA gene sequencing, metabolomic and metagenomic sequencing enabling even broader insights into the composition of uraemia retention molecules (URMs) and gut microbiota. There is strong evidence that there is an increased colonic generation or absorption of bacterial URMs in CKD [9,10].

The intestinal microflora maintains a symbiotic relationship with the host under normal conditions, but its imbalance occurs in chronic kidney disease (CKD). The pathogenic dysbiotic flora leads to an enhanced permeability of the intestinal barrier, allowing the passage of endotoxins and other bacterial products to the blood which has also been shown in CKD. By fermenting undigested products that reach the colon, the intestinal microflora produce indoles, phenols and amines, among others, that are absorbed by the host, accumulate in CKD and have harmful effects on the body. These gut-derived uraemic toxins and the increased permeability of the intestinal barrier in CKD have been associated with increased inflammation and oxidative stress and have been involved in various CKD-related complications, including cardiovascular disease and the progression of CKD. Moreover, specific factors that are produced endogenously by tissue metabolism or intestinal bacteria have been shown to be involved in the uraemic disturbed insulin signalling pathways [51,52].

The modification of the intestinal flora interferes with intestinal permeability, increasing the absorption of lipopolysaccharide (LPS) which are major components of the outer membrane of gram-negative bacteria. LPS activates inflammatory pathways by promoting expression of nuclear factor-kB (NF-kB) and mitogen-activated protein kinases (MAPKs) after binding to Toll-like receptor (TLR) 4/2 and receptor CD14 in innate immune cells and adipocytes and increases the production of TNF-α and interleukin-6 (IL-6) [47,53]. Both inflammatory cytokines (TNF-α, IL-6) through activation of serine kinases such as Jun N-terminal kinase (JNK), NF-kB, mammalian target of rapamycin (mTOR) induce IR by increased inhibitory serine phosphorylation of IRS-1 [47,53]. All these pathways are closely linked to changes in fatty acid uptake, lipogenesis and energy metabolism, which can lead to ectopic lipid accumulation in visceral tissues and impair insulin signalling through inhibitory serine phosphorylation of insulin receptor substrate (IRS).

In summary, the aetiology of IR in CKD is multifactorial. It includes a complex network involving immune system, inflammatory pathway, cytokines, adipokines, lipotoxicity and uraemic toxins, leading to an acquired defect of the insulin receptor-signalling pathway, especially via the inhibition of IRS-1 (Insulin receptor substrate) through serine residue phosphorylation [1,23,24].

Clinical Implications

Clamp studies have demonstrated IR in virtually all uremic subjects. Most nondiabetic patients do not develop persistent hyperglycemia, unless they have a genetic predisposition to diabetes [2,3]. In this setting, inadequate insulin secretion may combine with uremic insulin resistance to produce overt diabetes.

The hyperinsulinemia normally induced by insulin resistance may also contribute to the common development of hypertriglyceridemia in chronic kidney disease (CKD) Insulin enhances hepatic very low density lipoprotein (VLDL) triglyceride synthesis and may indirectly (via decreased sensitivity of lipoprotein lipase to insulin) reduce the rate of metabolism of VLDL.

Hyperinsulinemia can also affect fibrinolysis by stimulating the production of plasminogen activator inhibitor-1. It may therefore play a role in the decreased systemic fibrinolytic activity characteristic of CKD [54].

The expanding DNA/RNA sequencing technologies and knowledge of the chemical identity of the URMs have allowed us to make a step forward linking microbial-generated toxins to CKD-induced IR. This is of particular interest, since their production may prove simpler to suppress than the production of other waste solutes. Furthermore, the increasing knowledge of adipose tissue biology and its role in the regulation of energy metabolism have given rise to a unifying hypothesis such as the phenomenon of lipotoxicity linking ectopic lipid accumulation and IR. Although convincing in animal studies, whether dysbiosis or ectopic lipid accumulation is the cause of IR needs to be confirmed in human studies of CKD.

IR has also been implicated as one of the mechanisms of increasing cardiovascular risk (non-traditional).

Insulin requirements in diabetes mellitus

Insulin requirements show a biphasic course in diabetic patients with renal disease. It is not uncommon for glucose control to deteriorate as renal function deteriorates, as increasing insulin resistance can affect both type 1 and type 2 diabetics. Thus, insulin requirements may increase in the former, while the institution of insulin therapy may be necessary in the latter.

In comparison, the marked fall in insulin clearance in advanced renal failure often leads to an improvement in glucose tolerance. This may allow a lower dose of insulin to be given or even the cessation of insulin therapy [55,56]. Decreased caloric intake due to uremia-induced anorexia also may contribute to the decrease in insulin requirements [3].

With the institution of hemodialysis, the insulin requirement in any given patient will depend upon the net balance between improving tissue sensitivity and restoring normal hepatic insulin metabolism. As a result, one cannot readily predict insulin requirements in this setting, and careful observation with individualised approach is essential.

Hypoglycaemia

An unusual manifestation of disturbed glucose metabolism in chronic kidney disease (CKD) is the development of spontaneous hypoglycaemia [3,57,58]. This complication can be seen in both diabetic and nondiabetic subjects. In a retrospective analysis of almost a quarter million patients, the incidence of hypoglycemia was significantly higher among patients with CKD (defined as estimated glomerular filtration rate [eGFR] <60mL/min/1.73m2) compared with patients without CKD both among those with diabetes (2 fold higher risk) and without diabetes (1.5 fold higher risk) [59].

Multiple factors may play a contributory role. These include decreased caloric intake, reduced renal gluconeogenesis due to the reduction in functioning renal mass, impaired release of the counter regulatory hormone epinephrine due to the autonomic neuropathy of renal failure, concurrent hepatic disease, and decreased metabolism of drugs that might promote a reduction in the plasma glucose concentration, such as alcohol, propranolol and other nonselective blockers, and disopyramide [3,58].

Summary

• In patients with end-stage kidney disease, several disturbances in carbohydrate handling may be present. Tissue insensitivity to insulin is of primary importance, but alterations in insulin degradation and insulin secretion also may contribute.

• The kidney plays a central role in the metabolism of insulin in normal subjects. Insulin is freely filtered in the kidney. Of the total renal insulin clearance, approximately 60 percent occurs by glomerular filtration and 40 percent by extraction from the peritubular vessels.

• Impaired tissue sensitivity to insulin occurs in almost all subjects with end-stage kidney disease and is largely responsible for the abnormal glucose metabolism seen in this setting. There is also a dramatic reduction in insulin clearance that is also mediated by a concomitant decline in hepatic insulin metabolism. Further, insulin secretion tends to be blunted.

• Despite abnormalities in insulin metabolism, most nondiabetic patients with impaired kidney function, including end-stage kidney failure, do not develop persistent hyperglycemia, unless they have a genetic predisposition to diabetes.

• The aetiology of IR in CKD is multifactorial. It includes a complex network involving immune system, inflammatory pathway, cytokines, adipokines, lipotoxicity and uraemic toxins, leading to an acquired defect of the insulin receptor-signalling pathway, especially via the inhibition of IRS-1(Insulin receptor substrate) through serine residue phosphorylation.

• Among patients with diabetes and kidney disease, insulin requirements show a biphasic course. Glucose control commonly deteriorates as renal function deteriorates as increasing insulin resistance can affect both type 1 and type 2 diabetics. In comparison, the marked fall in insulin clearance in advanced renal failure often leads to an improvement in glucose tolerance. This may allow a lower dose of insulin, conversion to oral therapy, or even the cessation of insulin therapy.

• An unusual manifestation of disturbed glucose metabolism in chronic kidney disease (CKD) is the development of spontaneous hypoglycaemia. Multiple factors may play a contributory role [60-68].

Conclusion

The potential mechanisms by which important modifications of body homeostasis induced by the decline in kidney function affect insulin sensitivity needs to be confirmed in human studies with CKD. IR in CKD leaves its legacy on the vasculature and is with associated increased cardiovascular morbidity and mortality. This involves a complex crosstalk between the immune system, the inflammatory pathway, the metabolic pathway and their modulation via cytokines and uremic toxins. Future recent advances in this field will delineate the exact mechanism and provide novel therapeutic approaches to reduce IR associated cardiovascular mortality in CKD. The use of prebiotics, probiotics or synbiotics among other approaches could improve the increased permeability of the intestinal barrier in CKD and restore the gut disequilibrium.

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