Evidence for Increased Risk of Prediabetes in the Uremic Patient

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Key Words

Prediabetes risk · Uremia, prediabetic state · Inflammation, chronic renal failure · Insulin resistance

Abstract

A prediabetic state is defined as a higher than normal blood glucose level but not yet high enough to meet the diagnosis of overt diabetes mellitus. While patients with advanced diabetic nephropathy are vulnerable to hypoglycemia, we believe that there is sufficient evidence that uremic nondiabetic patients are susceptible to hyperglycemia, which calls for more attention that uremia is a prediabetic state. It is, therefore, intriguing to identify these uremic factors which lead to prediabetes. Such a study may have significance to improve uremic patients' outcomes. To raise the awareness of the uremic prediabetic state, this review will, therefore, elaborate on the analysis of factors important in the development of prediabetes in uremia and will delineate whether their modification leads to an improved patient outcome.

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Introduction

Prediabetes mellitus (PDM) can be defined as a state of abnormal glucose homeostasis, in which deficiency or resistance to insulin is the hallmark. Normal individuals

have strong compensatory mechanisms to protect the body against abnormal blood glucose levels. However, these compensatory mechanisms seem to falter in uremia. Therefore, uremic patients show vulnerability to both hypo- and hyperglycemia.

Table 1 shows the Canadian and American guidelines for the diagnosis of PDM [1, 2]. There was a gradient of mortality associated with abnormal glucose tolerance, ranging from a 40% greater risk in adults with PDM to a 110% greater risk in adults with clinically evident diabetes mellitus (DM). These associations were independent of the established cardiovascular disease risk factors [3]. PDM carries its own hazards, such as cancer mortality with a relative hazard of 1.87 as compared with 1.13 in diabetics [4] and a coronary heart disease risk 1.33 times higher than in the normal population [5]. Retinopathy characteristic of DM is present in 7.9% of PDM persons, while it is reported at 12.6% of diabetics [6]. In addition, PDM was reported to develop in 28% of the persons with a recent transient ischemic attack or ischemic stroke with no history of DM [7].

Much is known about renal failure caused by DM. On the other hand, considerably less interest has been given to the possible induction of hyperglycemia by chronic renal failure (CRF) and uremia. The disparity is likely caused by the tremendous health problems caused by DM. Intermittent or chronic low-grade hyperglycemia is not a benign condition. Further, the presence of hyper-

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glycemia and uremia may have a synergic deleterious impact on health. Therefore, the presence of PDM and uremia should receive more attention to improve patients' outcomes.

PDM is one component of the metabolic syndrome. The definition of the metabolic syndrome varies from one author to another. Therefore, to avoid the confusion, this article will focus only on PDM. To achieve our goal, we shall, therefore, elaborate on factors important for glucose metabolism in uremia, and special emphasis will be laid on the notion that CRF induces a prediabetic state.

Is Uremia a Prediabetic State?

There are many reasons to believe that uremia is a prediabetic state. For example, hyperinsulinemia, glucose intolerance, and dyslipidemia characterizing PDM are found in nondiabetic patients with (primary) kidney diseases even before the onset of impaired renal function and uremia [8].

In addition, disordered carbohydrate metabolism is widely recognized in patients with CRF [9]. These abnormalities most commonly include glucose intolerance in more than 50% of the azotemic individuals [10] and even overt fasting hyperglycemia [11]. On the other hand, an amelioration of the diabetic state with decreasing insulin requirements is a clinical concomitant of renal failure in patients with previously established DM [12]. Table 2 shows the possible causes of hypoglycemia in renal patients [13]. These contrasting data urged us to search whether or not uremia is a prediabetic state.

Prevalence of PDM in Uremia

Few researchers attempted to study the prevalence of PDM in uremia. For example, the prevalence of PDM in predialysis chronic kidney disease patients is 16% which increases with lower glomerular filtration rate in patients with moderate and advanced CRF [14].

In the Department of Nephrology, Saskatchewan University, we screened 252 uremic nondiabetic patients by fasting blood glucose. One hundred and twenty-nine patients (51%) were diagnosed with impaired fasting glucose according to the ADA 2007 guidelines [2]. In addition, 8 of the 252 patients who underwent oral glucose tolerance testing demonstrated impaired postprandial blood glucose, raising the prevalence of PDM to 54.36%.

Table 1. Guidelines for the diagnosis of PDM

CDA guidelines 2003 [1]			ADA guidelines 2007 [2]		
FBG mmol/l		2-hour PPBG mmol/l	FBG mg/dl		2-hour PPBG mg/dl
<i>PDM</i>					
6.1–6.9	plus	<7.8	100–125	plus	<140
<6.1	plus	7.8–11	<100	plus	140–199
6.1–6.9	plus	7.8–11	100–125	plus	140–199
<i>DM</i>					
≥7	or	≥11.1	≥126	or	≥200

CDA = Canadian Diabetes Association; ADA = American Diabetes Association; FBG = fasting blood glucose; PPBG = postprandial blood glucose; PDM = prediabetes mellitus; DM = diabetes mellitus.

Table 2. Mechanisms of hypoglycemia in renal patients

Deficiency of gluconeogenesis precursors
Impaired glycogenolysis
Diminished renal gluconeogenesis
Impaired renal insulin degradation and clearance
Poor nutrition
Deficiency in an immediate counterregulatory hormone such as catecholamine and glucagon

Mechanisms of Hyperglycemia in Renal Patients

In general, PDM may result from either impaired insulin action or decreased insulin secretion. Table 3 illustrates the possible mechanisms of PDM in uremia.

Impaired Insulin Action in Uremia

Insulin resistance (IR) is defined as diminished ability of cells to respond to the action of insulin in transporting glucose from the bloodstream into muscle and other tissues. Homeostasis model assessment of IR (HOMA-IR) is a proposed method to quantify the degree of IR:

$\text{HOMA-IR} = \text{fasting blood glucose (mmol/l)} \times \text{fasting insulin } (\mu\text{U/ml}) / 22.5$ [15].

Sit et al. [16] evaluated the prevalence of IR in 89 nondiabetic nonobese patients with chronic kidney disease. At HOMA-IR cutoff 5.4, they reported IR in 48.3% of their chronic kidney disease patients [16]. In another study [17], it was reported in 50% of such patients.

Table 3. Proposed mechanisms for hyperglycemia in uremia

Impaired insulin secretion	Impaired insulin action
Hyperparathyroidism	Retention of nitrogenous compounds in CRF
Activation of the RAS	Increased mediators secreted by adipose tissue: leptin and resistin
Enhanced expression of receptor for AGEs	Activation of the RAS
Increased oxidative stress	Anemia
Uremic dyslipidemia	Vitamin D deficiency
	Increased proinflammatory state

IR is present in patients with mild degrees of renal dysfunction or even in patients with apparently normal renal function, i.e., normal creatinine value and low glomerular filtration rate [18]. Thus, kidney disease per se seems to cause a syndrome of IR.

DeFronzo et al. [19] used the euglycemic insulin clamp technique in combination with titrated glucose and hepatic venous and femoral venous catheterization to examine the contribution of the liver versus peripheral tissues to the impaired insulin action observed in uremia. They concluded that suppression of hepatic glucose production by physiological hyperinsulinemia is not impaired and that insulin-mediated glucose uptake by the liver is normal in uremic subjects. Tissue insensitivity to insulin is the primary cause of IR in uremia.

The lack of correlation between insulin binding and tissue sensitivity to insulin suggests that the cellular mechanism accounting for the IR is probably the result of a defect in intracellular metabolism or in the glucose transport system [20]. There are several factors which explain the mechanisms of IR in uremia and are described below.

Retention of Nitrogenous Compounds

The dominant hypothesis is that nitrogenous compounds accumulating in CRF are the cause of a specific insulin-resistant state. This would explain the favorable effects of renal replacement therapy [21, 22] and low-protein diets [23]. McCaleb et al. [24] partly purified from uremic serum a peptide unique to uremia, which induced IR by a protein synthesis dependent mechanism. However, the effect of low-protein diets may not be specific, as low-protein diets improve IR in nonuremic diabetics [25]. The oral ingestion of a carbonaceous adsorbent reduces plasma glucose and insulin needs in uremic diabetic rats, highlighting the role of uremic toxins produced in the gastrointestinal tract [26]. There is a debate around the nature of these uremic toxins. Uric acid may be a candidate, as hyperuricemia is indeed an inherent component

of the metabolic syndrome and could also be used as a simple marker of IR even in nondiabetic nonuremic patients [27]. Others [28] suggested that hyperuricemia is not only a metabolic end product, but also a marker of a major pressor or pathogenic mechanism underlying the metabolic syndrome, and that leptin might be a regulator of serum uric acid concentrations in humans [28]. Pseudouridine, an outstanding nucleoside, which is not rebuilt into the tRNA once the parent tRNA is broken down, is another accused factor. Pseudouridine inhibits glucose utilization at the postreceptor level through lowering the intracellular Ca concentration [29]. A nonspecific binding reaction between cyanic acid formed from urea and protein or peptide is called carbamylation. Carbamoylated insulin is different from insulin in both biological and immunological activities [30]. Recently, it was shown that 1 of 15 carbamoylated amino acids, N-carbamoyl-L-asparagine, selectively reduced insulin-mediated glucose uptake in adipocytes [31].

Increased Mediators Secreted by Adipose Tissue

A large number of mediators (adipokines) are secreted from adipocytes. For example, leptin, resistin, adiponectin, adipsin, acylation-stimulating protein, angiotensinogen, tumor necrosis factor- α , interleukin (IL)-6, retinol-binding protein, plasminogen activator inhibitor-1, tissue factor, fasting-induced adipose factor, fibrinogen-/angiopoietin-related protein, and metallothionein. Some of these proteins induce IR, while others play a role in glucose and lipid metabolism; some are inflammatory cytokines, while others are involved in vascular hemostasis [32]. Uremia is also associated with elevation of some of the recently identified adipokines [33]. High leptin levels in CRF correlate with insulin levels [34]. Leptin mediates insulin insensitivity by an increase in the intracellular concentration of triglycerides [35]. It also may play a role in reducing glucose-stimulated insulin secretion, leading to glucose intolerance in CRF [34]. It is suggested that plasma resistin has a role in linking central obesity

and obesity-related IR to type II DM [36]. Of interest is also the finding of elevated resistin levels in patients with IgA nephropathy associated with lower glomerular filtration rate [37].

Indirect Mechanisms of IR in Uremia

Activation of the Renin-Angiotensin System (RAS). Recent studies made the intriguing observation that both pressor and subpressor doses of angiotensin II increase insulin-mediated glucose uptake in healthy subjects as well as in patients with type 2 DM [38]. The acute actions of angiotensin-converting enzyme (ACE) inhibitors on skeletal muscle glucose transport are associated with an upregulation of insulin signaling, including enhanced insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation and phosphatidylinositol-3-kinase activity, and ultimately with increased cell surface glucose transporter-4 (GLUT-4) protein. Chronic administration of ACE inhibitors or angiotensin-1 antagonists to insulin-resistant rodents can increase protein expression of GLUT-4 in skeletal muscle and myocardium [39].

Anemia. The treatment of anemia by erythropoietin leads to an increase in insulin-mediated glucose disposal [40]. It is suggested that treatment of anemia leads to improved exercise tolerance. Insulin sensitivity correlates with maximal aerobic capacity in CRF [41], and long-term exercise training reduces fasting blood glucose and insulin levels in hemodialyzed patients [42].

Vitamin D Deficiency. Insulin sensitivity shows an improvement after 3 months of treatment with 1,25-dihydroxycholecalciferol [43]. Rapid correction of metabolic acidosis raises the serum 1,25-(OH)₂D₃ levels in vitamin-D-deficient CRF patients and may underline the importance of maintaining normal acid-base homeostasis in the presence of secondary hyperparathyroidism in CRF [44]. Although these indirect mechanisms probably do not explain overall uremic IR, they have therapeutic implications.

Increased Proinflammatory State

The reasons of inflammation in CRF patients appear to be complex. The combination of an impaired immune response coupled with persistent immune stimulation may have a role in low-grade systemic inflammation and altered cytokine balance that characterizes the uremic state [45]. In this regard, it is becoming increasingly evident that CRF is characterized by a state of chronic inflammation that seems to be linked with oxidative stress, endothelial dysfunction, vascular calcification, and wasting [46]. Indeed, a wide array of inflammatory biomark-

Table 4. Common inflammatory markers known to be elevated in both uremia and PDM

Inflammatory marker	Reference
Fibrinogen	48
IL-6	49
CRP	50
Plasminogen activator inhibitor-1	51

ers, such as C-reactive protein (CRP), IL-6, and white blood cell (WBC) count, are strong predictors of outcome in CRF patients [47]. An increased proinflammatory state is also shown in prediabetic individuals who are predominantly IR. Multiple studies [48–51] have suggested that these risk factors may predict the development of type 2 DM, as shown in table 4. So, chronic inflammation emerges as a new nontraditional risk factor for the development of PDM.

Three ways have been suggested to interpret the link between these inflammatory markers and PDM. The simplest is that these markers may predict type 2 DM without being causal for the development of PDM and DM. The second aspect is that these cytokines may be a part of the atherogenic prediabetic syndrome. The third aspect is that inflammatory factors may be causal for type 2 DM, possibly through an intermediate variable, such as cytokines [52].

Recently emerged data supported the last proposal. Elevated CRP levels were associated with increased fasting insulin levels, fasting glucose levels, and HOMA-IR. CRP may cause IR by increasing IRS-1 phosphorylation at Ser³⁰⁷ and Ser⁶¹² via c-Jun N-terminal kinase and ERK1/2, respectively, leading to an impaired insulin-stimulated glucose uptake, GLUT-4 translocation, and glycogen synthesis mediated by the IRS-1/PI-3K/Akt/GSK-3 pathway [53].

Plasminogen activator inhibitor-1 is associated with incident DM, and its level further increases with the rising glucose levels and the development of DM [54].

In a prospective analysis, each of CRP, fibrinogen and plasminogen activator inhibitor-1 was a significant predictor of DM, and each factor remained significant in a multivariate model that included all three factors [55].

IL-6 impairs insulin signaling by reducing the expression of adiponectin in human adipose tissue and IRS-1 and GLUT-4 in 3T3-L1 cells [56, 57]. It is also a well-known inducer of suppressor of cytokine signaling (SOCS) proteins [58], and the induction of SOCS1 and

Fig. 1. Inflammatory mediators of PDM in uremia. PPAR- γ = Peroxisome-proliferator-activated receptor gamma; TNF- α = tumor necrosis factor alpha; IKK- β = I-kappa-B kinase beta; VC = vasoconstriction; BV = blood vessels. For explanation of the other abbreviations see text.

SOCS3 has been shown to inhibit insulin signaling by binding to the insulin receptor and IRS-1 [59–61]. In addition, IL-6 is a primary cytokine involved in hepatic CRP synthesis and a potent WBC differentiation factor [62], and both play a part in IR by their own mechanisms.

Similarly, IL-1 β is well known to activate the I kappa B kinase beta, leading to decreased expression of Glut-4, and markedly inhibits its translocation to the plasma membrane in response to insulin. This inhibitory effect is through a decrease in the amount of IRS-1 but not IRS-2 expression in both 3T3-L1 and human adipocytes [63]. Of interest, sensitizing insulin signaling by salicylates is induced via inhibition of the activity of I-kappa-B kinase beta [64]. Combined elevation of IL-6 and IL-1 β dramatically increased the expression of the acute-phase proteins, compared with the effect of each cytokine alone [65].

Multiple mechanisms have been suggested to explain the role of tumor necrosis factor alpha in IR. These include the downregulation of genes that are required for normal insulin action, direct effects on insulin signaling, induction of elevated free fatty acids via stimulation of lipolysis, and negative regulation of peroxisome proliferator-activated receptor gamma, an important insulin-sensitizing nuclear receptor [66].

In addition, the WBC count (indicative of systemic chronic inflammation) is positively associated with IR

[67]. Inflammation could increase the WBC count and, therefore, cytokine production which may decrease insulin sensitivity. Counterregulatory hormones such as cortisol and sex hormones have receptors on the surface of WBC and have been shown to play a role in their production and maturation [68]. This may explain the mechanism of IR by these hormones.

Inflammation-induced endothelial dysfunction alters endothelial cell permeability and diminishes peripheral blood flow which may limit insulin delivery, decreasing interstitial insulin concentration, the rate-limiting step for determining insulin effectiveness [69], and promotes IR [70].

From the above, we conclude that subclinical inflammation may be considered as a nontraditional potent risk factor for PDM through the release of different cytokines.

Impaired Insulin Secretion in Uremia

Another factor shared between PDM and uremia is the progressive inhibition of insulin secretion. This occurs in uremia due to several factors, as described below.

Hyperparathyroidism

Available data in dogs indicated that excess parathyroid hormone in CRF interferes with the ability of the beta cells to augment insulin secretion in response to the IR state without a change in the peripheral resistance to insulin. This effect of excess parathyroid hormone is not related to alterations in cyclic adenosine monophosphate production, but may potentially be due to calcium accumulation in the pancreas [71].

Pancreatic RAS

In the pancreas, recent evidence supports the presence of an islet RAS, which is subjected to activation. RAS molecule expression is sensitive to glucose concentration. Such a local islet RAS, if activated, may drive islet fibrosis and reduce islet blood flow, oxygen tension, and insulin biosynthesis. Moreover, activation of an islet RAS may drive the synthesis of reactive oxygen species, causing oxidative-stress-induced beta cell dysfunction and apoptosis, and thus contributes to the islet dysfunction. ACE inhibitors, and in particular zofenoprilat, protect human islets from glucotoxicity. These effects of ACE inhibition are associated with decreased oxidative stress [36]. Blockade of the RAS could contribute to the development of novel therapeutic strategies in the prevention and treatment of DM and in islet cell transplantation [72].

Preventing PDM by RAS inhibition may result from an improvement of beta cell function and/or an enhancement of insulin sensitivity, thereby decreasing the need for pancreatic insulin secretion [73]. Targeting RAS may lead to alterations in microcirculation and changes in Na^+ and K^+ concentrations across the cell membrane that could potentially affect both cellular insulin action and islet cell insulin secretion [74]. However, unexpected mechanisms might also play a role in such a protective effect of RAS inhibition, as newly recognized components of the RAS seem to modulate cardiovascular and renal regulation and as angiotensin appears to exert direct cellular effects [39].

Enhanced Expression of Receptor for Advanced Glycation End Products (AGEs)

In uremic plasma, accumulation of low-molecular-weight reactive carbonyl compounds such as 3-deoxyglucosone, dehydroascorbate, glyoxal, methylglyoxal, malondialdehyde, and arabinose derived from metabolism of carbohydrates, lipids, and/or amino acids has been noted as a general feature. The presence of these reactive AGE precursors in uremia, together with carbonyl-modified protein, has, therefore, been summarized as a state

of uremic carbonyl stress and accused as a major pathogenic mechanism and a risk factor for uremic end organ damage [75].

Receptors for AGE expression are upregulated in monocytes from patients with CRF. Enhanced levels of receptors for AGE may amplify AGE-induced monocyte perturbation and contribute to monocyte-mediated systemic inflammation in progressive CRF [76]. AGE levels in plasma and tissues increase independently of glycemia because diabetic and nondiabetic patients on chronic maintenance hemodialysis show similar total concentrations of serum AGEs. Moreover, AGE levels in uremic patients on hemodialysis were found to be several times higher than in patients with DM and a normal kidney function. Mechanisms other than hyperglycemia must, therefore, be involved additionally [77]. AGEs can directly upregulate the expression of the inflammatory prostaglandin-endoperoxide synthase-2 gene in pancreatic islets [78].

Oxidative Stress and Antioxidant Network

Oxidative stress appears to increase as CRF progresses and correlates significantly with the level of renal function [79]. On the other hand, an impairment of various intra- and extracellular antioxidant systems, which protect against harmful effects of free radicals, plays a significant role in development and exacerbation (or both) of oxidative damage in uremia and dialysis [80]. The glutathione (GSH) antioxidant system is among the antioxidant mechanisms frequently investigated in uremia [81]. Numerous studies have shown that uremic patients have significant reductions in red cell total GSH levels, as well as impairments in GSH-metabolizing enzymes. The decrease in GSH levels has been explained by an enhancement in the rate of GSH turnover. In addition, the depletion of other important antioxidants, such as vitamins C and E, adds cumulative effects that hamper GSH antioxidant activity and accelerate its depletion in uremic patients [82]. Oxidative stress induces beta cell dysfunction and apoptosis and thus contributes to the islet cell dysfunction.

Lipotoxicity and Elevated Free Fatty Acid Levels

The lipoprotein metabolism is altered in the majority of patients with renal insufficiency and CRF. It develops during the asymptomatic stages of renal insufficiency and becomes more pronounced as renal failure advances [83]. Hemodialysis patients show significantly increased concentrations of nonesterified fatty acids [84]. Increased levels of nonesterified fatty acids are accompanied by tri-

glyceride accumulation in parenchymal cells of multiple nonadipose tissues including skeletal and cardiac myocytes, hepatocytes, and pancreatic beta cells, resulting in chronic cellular dysfunction and injury in common disease states such as IR, pancreatic beta cell dysfunction, cardiomyopathy, and steatohepatitis. The general process has thus come to be termed lipotoxicity [85].

High concentrations of nonesterified fatty acids induce activation and enhanced expression of uncoupling protein-2 in mitochondria of pancreatic beta cells. Uncoupling protein-2 suppresses mitochondrial activation, and the adenosine triphosphate production normally gets induced by glucose. This limits the closure of plasma membrane adenosine triphosphate sensitive potassium channels, resulting in calcium influx required for insulin release [86].

Prevention of PDM in Uremia

The above discussion renders it clear that aggressive treatment of hyperparathyroidism, angiotensin-blocking treatment, and efficient dialysis modality are necessary for the well-being of renal patients in general and are conducive to decreasing the risk for PDM [21].

A number of drugs showed beneficial effects on IR in uremic patients such as ACE inhibitors and thiazolidinediones and vitamin D therapy and treatment of calcium and phosphate disturbances [87]. Of note, metformin should not be used in patients with moderate renal failure

because of the potential related, but rare, severe acidosis [88]. We are not aware of any specific study to address the potential impact of anti-inflammatory agents on the future development of PDM or overt DM in uremia. Further prospective studies would be necessary to test the safety and efficacy of pharmacological treatment for PDM patients.

Currently, there are well-known guidelines [1, 2] for the management of individuals with PDM and normal kidney function. To our knowledge, there are no similar guidelines for management of PDM renal patients. We believe that these current guidelines are acceptable and should be tested in the renal patients also.

Concluding Remarks

Over the last two decades, it became clear that the uremic state provides an environment for the impairment of several compensatory physiological responses, including insulin homeostasis. These abnormal responses contribute to further kidney damage possibly by mechanisms similar to those seen in patients with the metabolic syndrome. These impaired compensatory mechanisms also increase the cardiovascular morbidity and mortality seen in this patient population. Of added interest is the identification of pretransplant risk factors for the development of posttransplant DM. The contribution of uremic PDM in posttransplant DM warrants future investigation.

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