INSULIN RESISTANCE AND GLUCOSE HOMEOSTASIS IN PERITONEAL DIALYSIS

Paulo Cezar Fortes, Thyago Proença de Moraes, Jamille Godoy Mendes, Andrea E. Stinghen,
Silvia Carreira Ribeiro, and Roberto Pecoits-Filho

*Center for Health and Biological Sciences, Pontifícia Universidade
Católica do Paraná, Curitiba, Brazil*

Cardiovascular disease (CVD) is the main cause of death in peritoneal dialysis (PD) patients, a situation that can be explained by a combination of traditional and nontraditional risk factors for CVD in these patients. Glucose and insulin homeostasis are altered in chronic kidney disease (CKD) patients even in the early stages of CKD, leading to insulin resistance by various pathways. Several factors have been implicated in the pathogenesis of insulin resistance, including anemia, dyslipidemia, uremia, malnutrition, excess of parathyroid hormone, vitamin D deficiency, metabolic acidosis, and increase in plasma free fatty acids and proinflammatory cytokines. Insulin resistance and dyslipidemia are observed and increase with the progression of CKD, playing an important role in the pathogenesis of hypertension and atherosclerosis. Particularly in PD patients, exposure to glucose from dialysis fluid accentuates the foregoing metabolic abnormalities. In conclusion, insulin resistance and altered glucose metabolism are frequently observed in CKD, and although dialysis partly corrects those disturbances, the use of glucose PD solutions intensifies a series of harmful metabolic consequences. New therapeutic measures aimed at reducing metabolic disorders are urgently needed and perhaps will improve PD patient survival.

Perit Dial Int 2009; 29(S2):S145–S148   **www.PDIConnect.com**

KEY WORDS: Chronic kidney disease; insulin resistance.

Cardiovascular (CV) disease is the main cause of death in peritoneal dialysis (PD) patients, but the mechanisms mediating the increased CV risk observed in this group of patients are still largely unknown, which limits the perspective of effective therapeutic strategies. The leading hypothesis that tries to explain this high CV risk observed in PD patients is that they are already exposed to a number of traditional risk factors at initiation of chronic kidney disease (CKD). As renal dysfunction progresses, CKD-related risk factors are introduced, changing the profile both of the CV disease and of the risk markers. In this phase, the list of risk factors is expanded with mineral metabolism disturbances, anemia, fluid overload, uremic toxicity, and increased signs of oxidative stress and inflammation. Also, increases in insulin resistance and dyslipidemia are observed and rise with the progression of CKD. Also, potential additional harm is introduced after the initiation of PD, particularly because of the absorption of glucose. In this review, we analyze the available published data concerning glucose homeostasis and insulin resistance in PD patients.

GLUCOSE AND INSULIN HOMEOSTASIS IN CKD

Insulin regulates glucose homeostasis at many sites, reducing hepatic glucose output (by decreased gluconeogenesis and glycogenolysis) and increasing the rate of glucose uptake, primarily into muscle and adipose tissue. Insulin affects cells through binding to its receptor on the surface of insulin-responsive cells. The stimulated insulin receptor phosphorylates itself, and several substrates—including members of the insulin receptor substrate (IRS) family—initiate downstream signaling events. The inhibition of signaling downstream of the insulin receptor is a primary mechanism through which inflammatory signaling leads to insulin resistance (Figure 1).

Glucose metabolism is altered in CKD patients even in the earliest stages. Studies even in the 1980s showed that, although insulin secretion in CKD is normal, a decreased tissue sensitivity to insulin is responsible for the abnormal glucose uptake (1). In advanced CKD, particularly in stages 4 and 5, significant metabolic derangements in insulin metabolism occur. Interestingly,

Correspondence to: R. Pecoits–Filho, Center for Health and Biological Sciences, Imaculada Conceição, 1155, Curitiba PR 80215-901 Brazil.
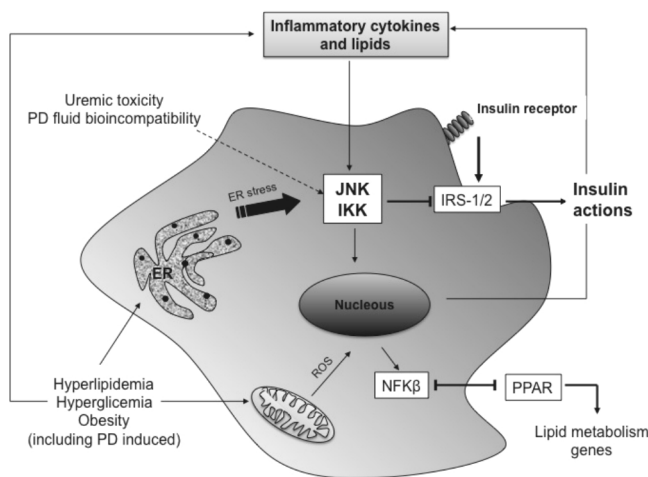r.pecoits@pucpr.br

Figure 1 — In patients on peritoneal dialysis (PD), uremic toxicity and factors related to peritoneal dialysis fluid bioincompatibility trigger the production of reactive oxygen species (ROS) and induce an inflammatory response through endoplasmic reticulum (ER). Hyperlipidemia, hyperglycemia, and obesity also induce production of ROS and amplify the inflammatory response. As a consequence, inflammatory pathways [Jun N-terminal kinase (JNK) and inhibitor of nuclear factor κB (NFKβ) kinase (IKK)] are activated, blocking insulin action and normal lipoprotein metabolism. This mechanism promotes a condition of insulin resistance and dyslipidemia. IRS = insulin receptor substrate; PPAR = peroxisome proliferator–activated receptor.

endogenous insulin is substantially degraded by the liver, but exogenous insulin is eliminated mainly by the kidney. Insulin is freely filtered at the glomerulus and extensively reabsorbed in the proximal tubule after enzyme degradation into smaller peptides. With the progression of kidney dysfunction, peritubular insulin uptake increases, compensating for the decline in the breakdown of filtered insulin. When the glomerular filtration rate reaches approximately 20 mL/min, insulin clearance decreases, and the half-life of insulin increases. Moreover, renal gluconeogenesis is markedly reduced in advanced CKD; weight loss as a result of wasting or appetite reduction is a common feature of this condition. Taken together, these metabolic disturbances lead to a decline in the requirement for exogenous insulin in advanced CKD.

Recent evidence showed that insulin is a anti-inflammatory hormone that suppress several proinflammatory transcription factors such as nuclear factor κB (NF-κB), early growth response protein 1, and activating protein 1, which all mediate inflammation. An impairment of the action of insulin because of insulin resistance would therefore result in the activation of these proinflammatory transcription factors and in an increase of the

expression of the corresponding genes (Figure 1). Derangements in other biologic effects of insulin could be associated with certain pathologic states in CKD such as hypertension and insulin resistance (2,3).

Numerous factors have been implicated in the pathogenesis of insulin resistance occurring before the initiation of dialysis therapy; examples include anemia, dyslipidemia, uremia, malnutrition, excess of parathyroid hormone, vitamin D deficiency, and metabolic acidosis. In this context, initiation of dialysis therapy should not be delayed, because evidence indicates that insulin resistance plays an important role in the pathogenesis of hypertension and atherosclerosis, important risk factors in patients with CKD. After the initiation of dialytic therapy, this situation is partially corrected.

However, particularly in PD patients, the development of insulin resistance after a initial improvement is generally attributed to a high glucose load absorbed from dialysis fluid, contributing to a wide spectrum of metabolic abnormalities including hypertriglyceridemia, poor glycemic control, new-onset diabetes, hypertension, and central obesity. An amplifying loop in the process of glucose absorption appears to be a consequence of the modifications in the peritoneum associated with a loss of ultrafiltration capacity.

Taken together, these abnormalities stimulate a cascade effect of inflammatory response, leading to a rise in mitochondrial production of reactive oxygen species (ROS). Production of ROS is enhanced, which causes further activation of inflammatory pathways. Several serine–threonine kinases, including Jun N-terminal kinase (JNK) and inhibitor of NF-κB kinase, are activated by inflammatory or stressful stimuli and contribute to the inhibition of insulin signaling. In response to stimuli such as endoplasmic reticulum stress, cytokines, and fatty acids, JNK is activated. Upon activation, JNK associates with and phosphorylates IRS-1, impairing insulin action (4). This sequence of events associating inflammation with insulin resistance, and vice versa, has known metabolic consequences as shown in Figure 1.

An increase in plasma free fatty acid (FFA) concentrations plays a key role in the pathogenesis of insulin resistance through specific actions that block insulin signal transduction. An increase in plasma FFA concentrations in normal-weight subjects to levels comparable to those seen in obese subjects also results in the induction of oxidative stress, inflammation, and subnormal vascular reactivity, and causes insulin resistance. The FFAs are released in abundance from an expanded adipose tissue mass. In the liver, FFAs produce glucose, triglycerides, and very-low-density lipoprotein (VLDL). Associated lipid and lipoprotein abnormalities include a reduction in

high-density lipoprotein (HDL) cholesterol and an increase in low-density lipoproteins. The FFAs also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglycerides. Increases in circulating glucose (and, to some extent, FFAs) raise pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity. It may also contribute to hypertension—as might increased levels of circulating FFAs.

Superimposed and contributory to the insulin resistance produced by excessive FFAs is the paracrine and endocrine effect of the proinflammatory state. Enhanced secretion of interleukin-6 (IL-6) and tumor necrosis factor α, among other cytokines, by a variety of cells in adipose tissue including adipocytes and monocyte-derived macrophages results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFAs. The IL-6 and other cytokines also are increased in the circulation and may enhance hepatic glucose production, production of VLDL by the liver, and insulin resistance in muscle. Cytokines and FFAs also increase the production of fibrinogen and plasminogen activator inhibitor 1 (PAI-1) by the liver, complementing the overproduction of PAI-1 by adipose tissue and resulting in a prothrombotic state. Reductions in the production of the anti-inflammatory and insulin-sensitizing cytokine adiponectin are also associated with metabolic syndrome and may contribute to the pathophysiology of the syndrome.

INSULIN RESISTANCE AND DIALYSIS MODALITY

Although efficacious as a chronic renal replacement therapy, PD exposes patients to a glucose load that could worsen the state of insulin resistance observed in patients with CKD. Disturbances of carbohydrate metabolism seem to be even more intense in nondiabetic PD patients than in hemodialysis patients. We recently observed that patients on PD had significantly higher fasting glucose, glycated hemoglobin (HbA1C), and homeostasis model assessment (HOMA) index values than did patients on hemodialysis (5). In addition, a recent study showed that, after PD initiation, a large number of patients developed new-onset hyperglycemia because of their exposure to hypertonic glucose solutions (6,7). In fact, glucose absorption through the peritoneum results in significantly higher serum glucose levels than are produced by an equivalent dose of oral dextrose. Insulin resistance can be safely assessed by HOMA index in

CKD patients, and a study showed that a high HOMA index predicts mortality in CKD patients (8).

EFFECT OF HIGH PERITONEAL SOLUTE TRANSPORT RATE ON METABOLIC COMPLICATIONS OF PD

Prolonged exposure of the peritoneum to hypertonic glucose solutions can damage the peritoneal tissue, inducing histologic and functional changes in the membrane. The peritoneal membrane of fast transporters present a large effective peritoneal surface area or higher intrinsic membrane permeability, and these patients are therefore prone to lose the osmotic gradient required for sustained ultrafiltration capacity. In addition, fast transporters absorb large quantities of glucose to the circulation. Longevity in PD (in terms of both technique and patient survival) is directly affected by transport characteristics, and patient and technique survival are both lower in patients with a high peritoneal solute transport rate. The metabolic alterations induced by fast transport potentially play a role in the development of CV disease in PD patients with a high peritoneal transport status (Table 1). Indeed, the association between metabolic syndrome and peritoneal solute clearance and transport rate has been recently reported (9).

THE IMPORTANCE OF GLYCEMIC CONTROL AND THE ROLE OF GLUCOSE SPARING

Improved glycemic control has the potential to reduce complications and improve outcomes. These benefits are observed in pre-dialysis patients and in patients under renal replacement therapy. Disturbances in glucose metabolism are also associated with poor prognosis in nondiabetic populations. Indeed, a recent study suggested that glycated hemoglobin is a predictor of all-cause

TABLE 1
Impact of High Peritoneal Transport Status on Metabolic and Cardiovascular Status in Peritoneal Dialysis Patients

Effect of increasing potential solute transport rate	Clinical consequences
Increased glucose absorption	Obesity
	Dyslipidemia
	Insulin resistance
Increased protein loss	Hypoalbuminemia
	Loss of antioxidant capacity
	Edema
Loss of ultrafiltration capacity	Fluid overload
	Hypertension
	Inflammatory activation

mortality in nondiabetic CKD patients, independent of other well-established risk factors (10).

As therapeutic options, peroxisome proliferator–activated receptor agonists (rosiglitazone, for instance) improve insulin resistance in diabetic and nondiabetic PD patients and also reduce levels of C-reactive protein, although an improvement in outcome has yet to be shown (11). Glucose-sparing solutions, such as those with amino acids or icodextrin, could potentially benefit both diabetic and nondiabetic PD patients by improving disturbances in carbohydrate metabolism (12). Ongoing and future studies will clarify whether glucose-sparing solutions are the best therapeutic approach to this important clinical problem.

CONCLUSIONS

Insulin resistance and altered glucose metabolism are frequently observed in CKD, and dialysis only partly corrects the disturbances. The use of glucose, the most common osmotic agent in PD solutions, intensifies a series of metabolic consequences that range from acute hyperglycemia and hyperinsulinemia to dyslipidemia and weight gain. New therapeutic measures are urgently needed to provide reductions in metabolic disturbances and perhaps to improve survival in PD patients.

REFERENCES

1. DeFronzo RA, Alvestrand A, Smith D, Hendler R, Hendler E, Wahren J. Insulin resistance in uremia. *J Clin Invest* 1981; 67:563–8.
2. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* 2005; 111:1448–54.
3. El-Atat FA, Stas SN, McFarlane SI, Sowers JR. The relationship between hyperinsulinemia, hypertension and progressive renal disease. *J Am Soc Nephrol* 2004; 15:2816–27.
4. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005; 115:1111–19.
5. Fortes PC, Mendes JG, Riella MC, Pecoits–Filho R. Carbohydrate metabolism disturbances in non-diabetic patients on peritoneal dialysis [Abstract]. *Perit Dial Int* 2006; 26(Suppl 2):S26.
6. Szeto CC, Chow KM, Kwan BC, Chung KY, Leung CB, Li PK. New-onset hyperglycemia in nondiabetic Chinese patients started on peritoneal dialysis. *Am J Kidney Dis* 2007; 49: 524–32.
7. Szeto CC, Chow KM, Leung CB, Kwan BC, Chung KY, Law MC, *et al.* Increased subcutaneous insulin requirements in diabetic patients recently commenced on peritoneal dialysis. *Nephrol Dial Transplant* 2007; 22:1697–702.
8. Shinohara K, Shoji T, Emoto M, Tahara H, Koyama H, Ishimura E, *et al.* Insulin resistance as an independent predictor of cardiovascular mortality in patients with end-stage renal disease. *J Am Soc Nephrol* 2002; 13:1894–900.
9. Chen HY, Kao TW, Huang JW, Chu TS, Wu KD. Correlation of metabolic syndrome with residual renal function, solute transport rate and peritoneal solute clearance in chronic peritoneal dialysis patients. *Blood Purif* 2008; 26:138–44.
10. Menon V, Greene T, Pereira AA, Wang X, Beck GJ, Kusek JW, *et al.* Glycosylated hemoglobin and mortality in patients with nondiabetic chronic kidney disease. *J Am Soc Nephrol* 2005; 16:3411–17.
11. Wong TY, Szeto CC, Chow KM, Leung CB, Lam CW, Li PK. Rosiglitazone reduces insulin requirement and C-reactive protein levels in type 2 diabetic patients receiving peritoneal dialysis. *Am J Kidney Dis* 2005; 46:713–19.
12. Takeguchi F, Nakayama M, Nakao T. Effects of icodextrin on insulin resistance and adipocytokine profiles in patients on peritoneal dialysis. *Ther Apher Dial* 2008; 12: 243–9.