**Insulin Resistance in Cardiovascular Disease, Uraemia and Peritoneal Dialysis**

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**Abstract**

Diabetic nephropathy is highly correlated with the occurrence of other complications of Type 1 and Type 2 diabetes, e.g. hypertension with cardiovascular disease (CVD) being the most frequent cause of death in patients with end-stage renal disease and undergoing renal dialysis. Hyperglycaemia and insulin resistance (IR) are responsible for the micro- and macrovacular complications of diabetes through different mechanisms. In particular, IR plays a key role in the aetiology of atherosclerosis both in diabetic and non-diabetic patients. Indeed, IR - exacerbated by organ-level selectivity - is more important than glycaemic control *per se* in determining cardiovascular outcomes. This may be exacerbated by the fact that IR is organ and pathway-specific due to only selective loss of sensitivity to insulin action of specific pathways/processes. Therefore, it is counterintuitive that using peritoneal dialysis (PD) in (frequently) diabetic renal disease patients should involve their exposure to high daily doses of glucose peritoneally. In view of the controversy about the causal association between glucose load and CVD in PD patients, we discuss the role that selective IR may play in the progression of cardiovascular disease in diabetic renal end-stage patients. In discussing these associations we propose that reducing glucose exposure in PD solutioins may be beneficial especially if coupled with strategies that address IR directly, and the avoidance of excessive use of insulin treatment in T2DM.

**Introduction**

Diabetic nephropathy is the leading cause of kidney disease in patients starting renal replacement therapy and affects ∼40% of Type 1 (T1D) and Type 2 diabetic (T2D) patients. It increases the risk of death, mainly from cardiovascular causes.  In diabetic patients, microvascular complications can be effectively prevented and their progression delayed by improving glycemic control, but this alone is not sufficient in reducing diabetic macrovascolar complications leading to CVD [1-3]. A key contributor to increased CVD risk in diabetic and non-diabetic patients is IR [1,2].

In addition to the insulin-induced downregulation of insulin receptor, IR arises from dysfunctional intracellular insulin signaling due to the activation of protein kinases and/or phosphatases that alter the activity of the kinases involved in the insulin signaling cascade [4]. IR does not occur for all insulin signalling pathways, with the result that those pathways still responding to insulin normally may be overstimulated because of the concomitant compensatory hyperinsulinemic condition experienced during the earlier stages of type-2 diabetes. This is the basis of selective IR and may be an exacerbating factor in the etiology of CVD and cardiuomentabolic risk in diabetes.

**Selective insulin resistance and increased cardiometabolic risk in diabetes**

Insulin affects a multiplicity of pathways and end-targets in most cell types through its multiple signaling mechanisms [5]. Insulin resistance may affect different cell types differentially in the same or separate tissues. Secondly, even within the same cell-type, different signaling pathways may become differentially resistant to insulin. Development of resistance to insulin action of only a subset of metabolic processes results in the establishment of vicious ‘push-pull’ cycles that result in further adverse metabolic sequelae. Some well-established examples will illustrate how selective IR can, over time, result in substantial deterioration of the metabolic profile of the patient and increase cardiovascular risk (Fig 1) .

**Selective insulin resistance in the liver**

A hallmark of T2D is the over-production of glucose by the liver owing to the resistance developed by hepatocytes to the anti-gluconeogenic and anti-glycogenolytic actions of insulin [6]. However, there is no concomitant decline in the responsiveness of de novo lipogenesis and triglyceride synthesis, nor of VLDL-triglyceride secretion by the liver [6] because these pathways are controlled by mechanisms that do not develop resistance to insulin [7]. During the development of T2D, they are overly stimulated because of the hyperinsulinemia due to the compensatory increase in pancreatic insulin secretion with the accompanying mobilization of fatty acids from adipose issue [8], results in the dual canonical markers (hyperglycemia, dyslipidemia) of the metabolic syndrome (Figure 2).

Selective IR in the liver is driven intracellularly by the loss of Akt-mediated phosphorylation - and inhibition - of Foxo1 leading to resistance to insulin inhibition of gluconeogenesis, whilst the direct and indirect activation of SREBP1c by insulin action are unimpaired with normal responsiveness of mTORC1 and its downstream target SREBP1c [9]. With systemic hyperinsulinemia, de novo lipogenesis and triglyceride synthesis and secretion are activated [10]. De novo lipogenesis in the liver is several-fold less sensitive to IR-mediated de-sensitization by hyperinsulinemia than gluconeogenesis and this appears to depend with the degree of prior exposure of the liver to insulin [11,12]. Interestingly, these observations highlight the importance of the link between hepatic de novo synthesis of fatty acids (DNL) and triglyceride synthesis and secretion. The unique role played by the enzyme diacylglycerol transferase 2 (DGAT2) as the link between hyperglycemia, steatosis and hypertriglyceridemia has been highlighted elsewhere [13].

**Selective insulin resistance in the kidney**

In the kidney, there is differential loss of insulin signaling in various parts of the renal tubule. Normally, insulin stimulates tubular Na+ re-absorption in an IRS2-dependent manner, and this is preserved in diabetes; however, IRS1 signalling is attenuated [14]. This results in the conservation of IRS2-dependent renal Na+ transport (with consequent hypertension and oedema), but diminished insulin-inhibition of IRS1-dependent renal gluconeogenesis by insulin - thus contributing to hyperglycaemia [15].

Podocytes too develop IR when exposed to hyperinsulinemia or to a diabetic environment e.g. in the db/db animal model of T2D [16]. IR in podocytes affects the function of nephrin which affects filtration barrier integrity and lowers podocyte glucose uptake [17]. Thus, selective preservation of aspects of insulin signaling in podocytes has the potential to impact several inter-connected metabolic pathways.

Intriguingly, in the proximal tubules specific ablation of carnitine acetyltransferase (CrAT), an enzyme that reversibly transfers the acetyl moiety of acetyl-CoA to carnitine in mitochondria, causes tubular injury, glomerulosclerosis, and kidney disease in mice [18]. Due to its capacity to buffer mitochondrial acetyl-CoA levels, CrAT plays a key role in intermediary metabolism. Indeed, acetyl-CoA is one of the most potent transcriptional and post-transcriptional regulators of key enzymes such as pyruvate dehydrogenase. Pyruvate decarboxylation is one of the most important determinants of the balance between the ulilization of the two major fuels (glucose, fatty acids). Disturbances in the balance between the utlilization of these two fuels underpin many of the consequences of the insulin-resistance syndrome [19]. The key role of CrAT in maintaining mitochondrial acetyl-CoA levels, compatible with a viable pyruvate dehydrogenase activity, is expected to counteract the effects of the hyperglycolytic phenotype [20]. Indeed, the inhibition of glycolysis by empagliflozin in proximal tubular cells remarkably reduces the mesenchymal transition, a key step in kidney and peritoneal fibrosis.

**Selective insulin resistance in the endothelium and heart**

The Ras/Raf-MAPK-ERK and the IRS-PI3K-Akt arms of the insulin signal transduction pathways too can become selectively resistant in vascular endothelial cells. Insulin can be either protective/anti-atherogenic (through the IRS/PI3K/Akt arm) or pro-atherogenic, through the Raf/MAPK/Erk cascade [21]. Through selective IR, the stimulation of NO production by insulin, normally mediated through IRS/Akt, becomes impaired, thus losing the vasodilatory effects of the hormone, whereas the MAPK-ERK pathway remains fully reponsive. Since this pathway stimulates the release of the vasoconstrictor endothelin-1, accompanied by an increased production of VCAM-1 (an adhesion molecule), this results in the promotion of atherosclerosis, thus shifting the effects of insulin towards a pro-atherogenic profile [21].

Selective IR also impairs cardiovascular integrity. Experimental hyperinsulinemia in mice induces a decrease of Akt signaling but preserves p44/42 MAPK activity, leading to a significant decrease in UCP3 expression in cardiac muscle [22]. UCP3 is thought to play a key role in protecting the heart against ischemia-reperfusion injury and to contribute towards ischemic preconditioning [23]. Moreover, excessive insulin signaling worsens cardiac function in a murine experimental model with IRS1 signaling but not the IRS2 being involved in exacerbating heart failure [24]. This is consistent with reports that sustained activation of upstream components of insulin signaling pathways result in pathological cardiac hypertrophy and subsequent heart failure [25].

**Integration of the effects on liver and heart**

Insulin may also exert its effects differentially and indirectly (non-autonomously) on the liver e.g. through its primary actions on the brain, and/or on adipose tissue [26]. Altered delivery of substrates from adipose tissue to the liver may play an important role in the differential sensitivity of gluconeogenesis and lipogenesis to the hyperinsulinaemia of diabetes [27]. In T2D patients, selective IR may compound their adverse cardiovascular clinical outcomes when the only therapeutic option is insulin injection. As suggested by Brown and Goldstein, when concluding an editorial on selective IR: “*By brute force treatment of type 2 diabetes patients with large doses of insulin, we can overwhelm the (selective) insulin resistance and control the blood sugar, but at what price?”* [28]. The price is a matter of an intense debate focused on the effects on dyslipidaemia [12] and the cardiovascular safety profile of exogenous insulin in type 2 diabetic patients [1-3, 21, 29, 30] even though glucose provides a minority of energy requirements of cardiac muscle itself.

**Insulin resistance, Renal Failure and Dialysis Modality**

There has been a longstanding recognition that uraemia is associated with IR [31]. The few euglycemic hyperinsulinemic clamp studies conducted on a small number of uremic patients have shown that shortly after the initiation of PD or HD there is a similar improvement in insulin resistance [32], although no longer-term follow up studies are available. Any demonstrable effect of peritoneal dialysis in improving IR may be obscured by relatively large insulin losses in the dialysate [33] and the presence of a severe insulin resistance at baseline in most CAPD patients [34]. These considerations may be complicated by changes in hepatic insulin clearance in end-stage kidney disease, and the effects of negative energy balance on glucose availability in these patients.

One of the few detailed studies to examine glucose metabolism in dialysis patients was conducted using oral glucose tolerance tests [35]. Transplant wait-listed dialysis patients had significantly lower insulin sensitivity than controls with normal renal function even when confounding variables were excluded. Therefore, underlying metabolic changes may be significantly underestimated when only glucose and glycated haemoglobin concentrations are measured. Of note, dialysis patients (HD or PD) showed a marked hypertriglyceridemia that was strongly associated with IR in multivariate analysis [35]. In a large prospective cohort of patients entering PD therapy, a simple proxy marker of IR - the product of plasma triglyceride and glucose - predicted CVD mortality risk [36].

An increased all-cause and CVD mortality risk associated with metabolic syndrome was found to be more pronounced in PD than in HD patients [37]. In addition, NAFLD, a condition driven by selective liver IR and associated with an high CVD risk, seems to be highly prevalent in PD patients, particularly in those receiving a greater glucose load through PD [38]. It should be emphasized that in non-dialysed type 1 and 2 diabetics, glycemic control (HbA1c) is not a good predictor of CVD, possibly because these patients may be malnourished and/or because of the presence of subclinical/clinical anemia that affect red blood cell survival particularly in CKD patients, whereas IR is predictive of CVD and indeed may be the most important single cause of coronary artery disease in non-diabetic individuals [1, 2, 38-41].

An interesting surrogate marker is the incidence of new-onset diabetes during the course of dialysis treatment; in some studies this appears to be higher in HD patients [42], despite several reports of undiagnosed or incident diabetes in PD patients [43,44]. This is consistent with a number of studies demonstrating increases in fat mass or body weight during PD [45,46] but suggests that similar changes occur in the HD population who are not exposed dialysate glucose. However, a recent study [47] has shown that the incidence of new-onset diabetes was higher in PD patients than in HD patients with a hazard ratio of 1.51 (95% CI 1.30–1.75) for PD patients (the HR in using propensity score matching was even higher). This study also showed that among PD patients, the incidence was lower in icodextrin users than in non-users with an adjusted HR of 0.66 (95% CI 0.50–0.88) for users. Interestingly, the risk of new onset diabetes after kidney transplantation seems to be higher in PD than HD patients [48]. A recent meta-analysis suggested that up to 32% of PD patients develop a glucose disorder after the initiation of PD therapy, though the incidence of DM between PD (8%) and HD (9%) was not meaningfully different [ref]. As correctly pointed out by the authors of the meta-analysis, most of the studies analyzed were focused on indices such as fasting blood glucose levels that are poorly informative with regard to insulin resistance.

**Potential adverse effects of glucose exposure in patients undergoing PD**

Although the lesser used dialysis modality, PD offers several advantages e.g. a more gradual and continuous fluid and solute clearance, improved preservation of residual renal function, minimal cardiac stress, and a higher cost effectiveness for a similar survival benefit [49]. But PD has some complications, including peritonitis and peritoneal membrane damage contributing to relatively high rates of death, particularly through cardiovascular disease. One of the drivers of these adverse outcomes is thought to be the continuous exposure of the peritoneal membrane to high glucose concentrations - a constant insulin-secretagogue stimulus. This may not only aggravate IR in diabetic PD patients, but exacerbate the detrimental systemic sequelae of selective IR, and thus, micro- and macro-vascular consequences. Glucose degradation products (GDPs) generated during the sterilization process of PD solutions, as well as high lactate, low pH levels and glucose itself have been implicated in the pathogenesis of adverse functional changes in the peritoneal membrane [50].

“Non-glucose” and “biocompatible” PD fluids have been developed with the aim of improving ultrafiltration, and reducing both the metabolic abnormalities, and the functional and anatomical changes in the peritoneal membrane that occur with conventional PD fluids [51 and ref]. In diabetics with a high-average peritoneal transport rate randomization to icodextrin-based PD solution resulted in reduced glucose absorption, insulin need, fasting glucose, triglycerides and HbA1c levels, suggesting that reducing glucose peritoneal absorption improves metabolic control in PD patients with a fast absorption rate of glucose [ref]. , In addition, the use of icodextrin solution is associated with improved peritoneal ultrafiltration, a reduced risk of fluid overload, and no increase in risk of adverse events [52]. Amino acid-based solutions were developed for improving the nutrition and metabolic status of PD patients.

However, clinical trials on more biocompatible PD solutions have failed to show a consistently beneficial action on peritoneal membrane function and ultrafiltration [53,54].

**Evidence** **linking peritoneal dialysate glucose loading to insulin resistance**

The impact of dialysate glucose on IR may depend on glucose loading over a prolonged period. In the IMPENDIA-EDEN trial [55], a low dialysate glucose load showed a small but significant reduction in dyslipidemia despite no demonstrable difference in weight or insulin requirement. Conversely, diabetic/non-diabetic patients, randomized to either a biocompatible/amino acid/Icodextrin regime with a lower dialysate glucose or conventional solutions with normal dialysate glucose, showed no difference in body weight, plasma triglycerides, HDL-cholesterol, or fasting glucose levels [56]. In the STARCH trial [57], the use of icodextrin resulted in a reduction in insulin requirement, but there was no demonstrable difference in HbA1c. A novel approach to improving insulin resistance in non-diabetic CAPD patients might be represented by enrichment of the dialysate with L-carnitine, as suggested in a proof-of-concept randomized controlled trial by the significant improvement in insulin sensitivity (measured by euglycemic hyperinsulinemic clamp) after a 4-month switching from a standard glucose-based PD solution to the enriched experimental solution [34].

In a cross-sectional study of 51 non-diabetic prevalent PD patients, there was no association between peritoneal glucose and HOMA-IR, BMI or relative fat mass [58], although another longitudinal study of 195 incident Chinese PD patients found that dialysate glucose loading was associated with increased BMI, hypertriglyceridemia and lower HDL-cholesterol [59]. Observational studies and a double-blind randomized controlled trial have also suggested that Icodextrin usage, but not dialysate glucose load *per se*, is associated with lower adiposity [60 and ref]. Increased dialysate glucose load has been shown to predict higher random glucose levels [43]. Patients with a higher peritoneal glucose absorption had an increased risk of 2-year cardiovascular mortality independent of other cardiometabolic risk factors [61].

**Evidence linking Insulin Resistance to cardiovascular outcomes**

**Insulin** **resistance versus glycaemic control in type 2 diabetes and the general population**

Large RCTs on diabetics, including the ACCORD, ADVANCE and VADT trials, have failed to demonstrate any improvement either in the risk of mortality or of most macrovascular complications despite better glucose control [30]. However, in T2D a pathophysiological link between IR and mortality may not be entirely mediated by hyperglycaemia [1,2]. In addition, a recent retrospective cohort study has shown that insulin and sulfonylureas are associated with an higher cardiovascular risk when used as second-line medications in adult T2D patients [29].

Therefore, targeting insulin resistance rather than the consequent hyperglycaemia may have the greatest effect in reducing cardiovascular mortality/morbidity [40]. Even in T1D, the most predictive cardiovascular risk factor remains IR rather than glycated hemoglobin [41]. Interestingly, SGLT2 inhibitors, which improve IR and reduce systemic insulin exposure through glycosuria result in a significant reduction in all cause and cardiovascular mortality in T2D [62,63].

**Insulin** **resistance versus glycemic control in the dialysis population**

The mode of action of SGLT2 inhibitors is, conceptually, not that dissimilar to replacing dialysate glucose in PD with a more biocompatible osmotic agent. Constant glucose loading and concomitant insulin secretion in PD suggest that hyperinsulinemia *per se* may be involved in the development of IR both in humans and rodents [64], similar to pharmacological treatment with insulin [65,66]. The inhibition of insulin secretion with diazoxide attenuates hyperinsulinemia, reduces adiposity and improves insulin sensitivity without inducing hyperglycemia [67]. In small studies, IR was associated with cardiovascular deaths [68] but not in all studies [69]. The leptin-adiponectin ratio was associated with mortality in one study [70] but previous studies of IR in mild to moderate CKD showed inconsistent associations between mortality and IR [71].

Obesity is consistently associated with a better outcome in HD [72], but no consistent effect was found in PD patients [73]. Similarly, higher triglyceride levels are associated with a lower mortality in haemodialysis patients [74] but for PD, the findings have been mixed, with reports of increased [75], decreased [76], and U-shaped [77] associations between hypertriglyceridaemia and mortality.

Selective IR would also affectresidual kidney function in dialysis patients (see section 2c). Nevertheless, results have beem variable [78] particularly with respect to cardiovascular mortality [79-81].

Supporting a role for hyperglycaemia as a driver of mortality in diabetic HD patients, one meta-analysis [82] demonstrated a hazard ratio of 1.29 (95% CI 1.23-1.35) for HbA1c of >69mmol/mol) but low HbA1c levels (<54mmol/mol) were also associated with worse outcomes especially in incident patients (HR 1.29, 95% CI 1.23-1.35). This U-shaped association of HbA1c and mortality has been demonstrated in PD patients too [83] so it is unlikely that stringent reductions in HbA1c will meaningfully reduce dialysis patient mortality, especially given the findings in the non-dialysis diabetic population.

Some studies have addressed this question by assessing the relationship between dialysate glucose load and mortality. Although these studies did find that a higher peritoneal glucose load was associated with higher all cause and CVD mortality [84], it is difficult to infer a definitive causal relationship. When using skin autofluorescence (SAF) to evaluate the accumulation of advanced glycation end products as a marker linked to increased glucose exposure PD patients had significantly higher SAF values in each category of age and dialysis duration, regardless of the presence or absence of diabetes compared to HD patients [85]. SAF was also remarkably associated with PD duration and glucose exposure and independently associated with CVD. However, other studies have shown that SAF and a marker of vascular stiffeness could independently predict mortality [86] although with respect to the CVD risk calculated according to the Framingham’s risk score [87], the additional contribution of SAF and vascular stiffeness to the calculated risk was relatively modest.

**Conclusions**

A clear relationship links hyperinsulinemia to insulin resistance and increased risk of CVD [1-3]. Indeed, although in T1D there is the additional element of insulin deficiency, the increased risk of CVD has been attributed to peripheral hyperinsulinemia due to exogenous insulin treatment [41,64]. Selective insulin resistance exacerbates pathological sequelae, and in patients with renal failure, who already demonstrate significant insulin resistance this may be exacerbated by glucose-based PD therapy. In addition, diabetic PD subjects are even more susceptible as, progressively, the only therapeutic option for these patients is insulin treatment. This not only reinforces the desirability of lowering the glucose content of PD solutions but also to investigate new antidiabetic therapeutic options able to exert pharmacological actions without the direct involvement of insulin administration.

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**Figure legends**

**Figure 1**. Clinical effects of insulin resistance on the endothelium, cardiac muscle and hepatic metabolism. The high degree of continued activation of the pathways, illustrated in each text-box, that remain insulin sensitive under otherwise insulin resistant states results in important elements of the metabolic syndrome that contribute towards the associated increased incidence of cardiometabolic risk.

**Figure 2.** Suggested mechanisms through which selective retention of insulin signaling to de novo lipogenesis is achieved in hepatocytes under conditions of hyperinsulinemia induced during whole-body insulin resistance. Hepatic selective insulin resistance results in canonical characteristics of the metabolic syndrome, namely hyperglycemia and dyslipidemia.

**Figure 3.** Continued sensitivity of the GRB2 arm of insulin signalling in the endothelium, but not of the IRSs arm, results in an imbalance between the pro- and anti-atherogenic effects of insulin (and growth factors) on the endothelium, favouring atherosclerosis.