REVIEW ARTICLE

Insulin resistance as a novel therapeutic target in patients with chronic kidney disease treated with dialysis

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KEY WORDS

ABSTRACT

chronic kidney disease, dialysis, insulin resistance, renal replacement therapy Clinical significance of insulin resistance in patients with chronic renal failure treated with dialysis has not been fully elucidated and requires further research. The available data indicate that long-term dialysis therapy promotes the development of insulin resistance. Furthermore, it has been proven that insulin resistance in this patient group is a strong independent predictor of mortality from cardiovascular causes. Insulin resistance as a potential modifiable cardiovascular risk factor should be considered as a novel therapeutic target in patients undergoing both hemodialysis and peritoneal dialysis.

Increased resistance to insulin in patients with kidney failure was first reported in the late 1970s. Subsequently, a study published by DeFronzo et al. in 1981 demonstrated that resistance to insulin in patients with chronic kidney disease (CKD) developed mainly in peripheral tissues. At the same time, no impairment of hepatic glucose uptake or inhibition of glucose synthesis in the liver were observed.¹ Currently, it is known that insulin resistance develops simultaneously with the decrease of glomerular filtration already in the early stages of CKD. Numerous factors related to CKD have been implicated in the etiology of insulin resistance. These include uremic toxins (enhanced protein carbamylation), chronic metabolic acidosis, intracellular ion homeostasis disequilibrium, as well as qualitative and quantitative disturbanc-

Chronic kidney disease and insulin resistance

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adipocytes (adipocytokines), chronic inflammation as well as low physical activity.² A prospective study published by Shinohara et al. in 2002 demonstrated for the first time that insulin resistance is an independent predictor of mortality from cardiovascular causes in patients with end-stage renal disease without coexisting diabetes. It was shown that the influ-

ence of insulin resistance on cardiovascular risk

es of insulin receptors on adipocytes, skeletal mus-

cle cells and hepatocytes, cytokines produced by

is independent of age, body mass index (BMI), concomitant hypertension, dyslipidemia, or C-reactive protein (CRP) levels. Interestingly, no significant correlation between insulin resistance and mortality from noncardiovascular causes was observed.³

Initiation of renal replacement therapy by dialysis in patients with irreversible kidney failure has long been suggested to have a positive effect on the reduction of insulin resistance in this group of patients. In 2000, Kobayashi et al. reported an improvement in insulin resistance markers irrespective of whether the patients were undergoing hemodialysis (HD) or peritoneal dialysis (PD).⁴ Of note, however, this particular study described improvement in insulin resistance that developed during the initial 5 to 6 weeks of dialysis, and did not address the long-term effect of HD or PD on this parameter.

Insulin resistance, as a potentially modifiable cardiovascular risk factor, is currently considered as a therapeutic target in patients undergoing dialysis. In recent years, preliminary reports regarding a potential modification of insulin resistance in patients on long-term dialysis have been published.

Insulin resistance and renal replacement therapy by peritoneal dialysis One of the main objectives of

PD is to treat hypervolemia. Removal of excess water from the patient's body occurs mainly by osmotic ultrafiltration. The substance that creates osmotic gradient is glucose present in the dialysis solution, thus making the water from vascular bed flow to the peritoneal cavity as a solution compartment. Depending on the required ultrafiltration rate, solutions containing 1.36%, 2.27%, or 3.86% of glucose or 1.5%, 2.5%, 4.5% of its monohydrate form can be used. In order to achieve effective hypervolemia treatment in patients with progressive loss of residual renal function, dialysis solutions with higher glucose concentrations are used. Alternatively, icodextrin, an osmotically active glucose polymer obtained from starch, can be used instead of glucose.⁵ Depending on the duration of exposure of the peritoneal membrane to dialysis solution, 80% or more of glucose present may be absorbed into the bloodstream. Therefore, it can provide approximately 100 to 300 g of glucose load with energy content that constitutes 14% to 34% of the daily requirement. Continued absorption of glucose from the dialysis solution may cause a number of metabolic disorders, particularly in patients characterized by rapid transport through the peritoneal membrane. Metabolic complications of increased glucose absorption include induction or aggravation of carbohydrate and lipid metabolism disorders, such as hyperlipidemia, obesity, hyperglycemia, as well as hyperinsulinemia and insulin resistance, together with their potential clinical consequences. Recently, it has been suggested that the glucose load delivered with PD solutions stimulates chronic insulin secretion, thus leading to hyperinsulinemia and increase of insulin resistance during long-term PD therapy. In 2005, Tuzcu et al. compared the progression of insulin resistance in patients undergoing renal replacement therapy (RRT) with either HD or PD.⁶ The study included 45 patients treated with continuous ambulatory PD (CAPD) and 51 patients with HD. The control group comprised 50 healthy individuals. It was shown that the insulin sensitivity index, measured by homeostasis model assessment of insulin resistance (HOMA-IR), was statistically significantly lower (P < 0.002) in patients on PD than in those on HD or in the control group.⁶ These results indicate that the use of glucose solutions in PD facilitates the development of insulin resistance. In order to overcome that problem, Amici et al. conducted a study in 2001 using icodextrin as an alternative solution to glucose. The study included 27 patients on PD, without diabetes. In 15 patients, the alternative solution was used for the overnight exchange, while the remaining 12 patients were treated with standard glucose solutions. In the first group, it was observed that serum insulin levels were statistically significantly lower, while the insulin sensitivity index by HOMA was higher.⁷ Similar findings were published by Canbakan et al. in 2007.8 Furthermore, the report by Takeguchi et al. in 2008 showed

that replacement of glucose solution with icodextrin for the overnight exchange resulted in statistically significantly lower fasting insulin levels and the insulin resistance index in patients who had HOMA-IR index of >2 at baseline (prior to icodextrin inclusion).⁹ These results indicate that the long-term use of dialysis solutions containing icodextrin for the overnight exchange reduces hyperinsulinemia and increases tissue insulin sensitivity in patients on CAPD.

Development of insulin resistance in PD patients might be counteracted pharmacologically. For example, rosiglitazone, a peroxisome proliferator-activated receptor- γ (PPAR- γ) agonist, has already undergone a preliminary evaluation. This particular interest in PPAR- γ as treatment targets comes from their role as transcription factors that regulate the expression of genes involved in the differentiation and proliferation of adipocytes, lipid metabolism, insulin resistance regulation, and apoptosis. In a study conducted by Lin et al., with healthy volunteers as the control group, rosiglitazone was used in patients with nondiabetic nephropathy, treated with PD, at a dose of 4 mg daily for 12 weeks. A significant (P < 0.05) reduction in insulin resistance as measured by the HOMA-IR index was observed.¹⁰ It is still unclear whether PD modifications such as CAPD or automatic PD (APD) may affect the development of insulin resistance. In APD, the glucose load originating from the dialysis solution is particularly large at night-time leading to constant stimulation of insulin secretion (multiple changes of the dialysis solution performed by the cycler). Additional stimulation occurs during the day (meals as well as an additional daily peritoneal exchange). Further comparative studies are certainly needed to elucidate whether the choice of CAPD vs. APD could determine the risk of insulin resistance in patients treated with PD.

Insulin resistance and renal replacement therapy by hemodialysis As noted above, initiation of HD had a similar impact on insulin resistance to PD.⁴ Several studies are currently underway in order to determine which therapeutic interventions may lead to the reduction of insulin resistance in patients on HD. For example, the type of dialyzer, treatment with either recombinant human erythropoietin (rHuEpo) or angiotensin receptor type 1 (AT1) antagonists may all potentially have an influence on insulin resistance.

Insulin resistance and recombinant human erythropoietin in patients on hemodialysis A potential association between insulin resistance and anemia, secondary hyperparathyroidism, anthropometric markers, inflammation markers, and the left ventricular posterior wall thickness has recently been analyzed in HD patients. Sit et al. enrolled 57 nondiabetic patients with normal BMI (those with BMI >25 kg/m² were excluded). The patients were divided into 2 groups, depending on the HOMA-IR index (1.23 was adopted as the cut-off value). No effects on insulin resistance as measured by HOMA-IR were observed for such factors as BMI, dialysis adequacy markers, parathyroid hormone level, inflammation markers, or left ventricular posterior wall thickness on echocardiography. However, it was found that patients with HOMA-IR <1.23 had higher hematocrit values and significantly lower (P <0.05) weekly requirement for recombinant human erythropoietin, as compared to those with HOMA-IR >1.23.¹¹

Another study has examined the effects of rHuEpo treatment on insulin resistance in patients without diabetes treated with HD. The study included 3 groups of patients: on HD and receiving rHuEpo, on HD but with no rHuEpo administration, and healthy volunteers. It was found that the HOMA-IR index was significantly higher in the group not receiving rHuEpo. Furthermore, there was a positive correlation between the duration of rHuEpo use and insulin sensitivity in patients on HD.¹²

Hemodialysis with the use of high-flux dialyzers

The high-flux dialysis technique was introduced over 20 years ago and the initially employed membranes were made of modified cellulose. Subsequently, cellulose gave way to synthetics (polysulfone, polyamide, polymethylmethacrylate), and nowadays such synthetic membranes are used exclusively. They are able to remove substances of molecular weight up to 20,000-30,000 daltons including, for example, β_2 -microglobulin. Efficiency of high-flux HD can be improved by increasing blood and dialysis solution flows (>500 ml/min and 700-800 ml/min, respectively). Notably, the method of high-flux HD is particularly beneficial for patients with higher body weight (>75 kg). In this particular patient population, it ensures proper dehydration, dialysis dose (high urea clearance), and relatively high middle--molecule clearances, as compared with classic dialysis. Some authors have found higher hemoglobin levels in patients on high-flux HD that required lower erythropoietin dose. Furthermore, no increased oxidative or carbonyl stress have been observed with the use of high-flux membranes, while a positive effect on the blood lipid profile has been demonstrated. Follow-up studies have shown lower morbidity in patients treated with high-flux as compared with low-flux dialysis. The prospective HEMO study demonstrated that patients undergoing dialysis treatment for more than 44 months had more benefits mostly from the use of high-flux dialyzers. Moreover, they showed the lowest mortality rate from cardiovascular causes, independent of the duration of dialysis treatment.¹³

The preliminary reports on the effects of high-flux dialyzer on insulin resistance are particularly promising. In a study conducted by Chu et al., patients on HD have been randomized into 2 groups, for which 2 different types of dialyzers were used: the F8 HPS (low-flux) membrane in the first group and FX 80 (high-flux) in the other. During a 2-month, prospective follow-up, no significant differences in the adiponectin, CRP, prostaglandin $F_{2\alpha}$, glucose or insulin levels were found, as compared with the baseline values. However, a significantly lower HOMA-IR index was observed (P = 0.02) in the group treated with high-flux membranes.¹⁴

Insulin resistance and angiotensin receptor type 1 antagonists in patients on hemodialysis Several studies have indicated that AT1 receptor antagonists improve insulin sensitivity in patients with hypertension. The metabolic outcome of their action seems to be associated with their partial agonist effect on PPAR-y. It remains to be seen whether a similar result of the use of AT1 receptor antagonists may be obtained in patients undergoing HD. Interestingly, preliminary results of a 12-week use of valsartan in patients on HD showed a significant reduction of both fasting insulinemia as well as the HOMA-IR index (P = 0.005).¹⁵ Still, further studies are needed to evaluate the effects of different AT1 receptor antagonists on insulin resistance.

Summary Long-term RRT with both HD and PD promotes development of insulin resistance. Insulin resistance in these groups of patients is a strong independent predictor of mortality from cardiovascular causes. Insulin resistance, as a potential modifiable cardiovascular risk factor, should be considered as a novel therapeutic target in patients on HD or PD. Potential intervention that might decrease insulin resistance in patients treated with PD is the reduction of glucose load in dialysis solutions, for example by using icodextrin. Introduction of PPAR- γ agonists may provide another approach in PD patients. In patients treated with HD the use of high-flux dialyzers, AT1 receptor antagonists, rHuEPO, and effective correction of anemia may be considered as potential factors decreasing insulin resistance. However, it should be emphasized that the available data are derived from few short-term studies conducted on small groups of patients.

Therefore, further research is required to prove the effect of these interventions on decreasing insulin resistance, as it remains an important cardiovascular risk factor in patients treated with HD and PD.

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ARTYKUŁ POGLĄDOWY

Insulinooporność jako nowy cel terapeutyczny u chorych z przewlekłą chorobą nerek poddawanych dializoterapii

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SŁOWA KLUCZOWE STRESZCZENIE

dializa, insulinooporność, leczenie nerkozastępcze, przewlekła choroba nerek

Znaczenie kliniczne insulinooporności u chorych z przewlekłą chorobą nerek leczonych nerkozastępczo nie zostało wystarczająco wyjaśnione i wymaga dalszych badań. Dane z piśmiennictwa wskazują, że przewlekła dializoterapia może sprzyjać rozwojowi insulinooporności. Jednocześnie wykazano, że insulinooporność w tej grupie chorych jest niezależnym silnym predyktorem zgonu z przyczyn sercowonaczyniowych. Jako potencjalny poddający się modyfikacji czynnik ryzyka sercowo-naczyniowego, insulinooporność powinna być traktowana jako nowy cel terapeutyczny u chorych poddawanych zarówno hemodializom, jak i dializie otrzewnowej.

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