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CLINICAL STUDY

The effect of two different high-flux dialysis membranes on insulin resistance in non-diabetic end-stage renal disease patients

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Abstract

Objective: The aim of this study was to investigate the effect of two different types of high-flux dialysis membranes on insulin resistance among patients who are receiving hemodialysis (HD) due to end-stage renal failure (ESRF). *Materials and methods*: Forty-six (21 female, 25 male) patients were included in the study, who were on HD treatment due to stage-5 chronic renal failure. Prior to the study, fasting insulin resistance via Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) and fractioned urea clearance (*Kt/V*) values were calculated using the urokinetic model. The polysulfone (PS) dialysis membrane of all patients included in the study was replaced with ''polyarylethersulfone, polyvinylpyrrolidone, polyamide (PPP)'' high-flux membrane that has the same surface area over 12 weeks. At the end of the 12-week period, HOMA and *Kt/V* values were recalculated. *Results*: At the end of the 12-week period, *Kt/V* values rose statistically significant from 1.575 to 1.752 ($p = 0.002$). HOMA-IR values declined, though not statistically significant, from 3.268 to 2.926 ($p = 0.085$). PPP high-flux membrane increased the *Kt/V* values significantly compared to the PS membrane, while it decreased the insulin resistance and increased insulin sensitivity. *Conclusion*: The two different types of high-flux dialysis membranes used for HD have different effects on insulin sensitivity. Compared to the PS membrane, PPP high-flux membrane decreased insulin resistance by increasing insulin sensitivity among non-diabetic ESRF patients.

Keywords

Dialysis membranes, end-stage renal disease, high-flux, insulin resistance

History

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Introduction

Among chronic renal failure patients, cardiovascular diseases are considered to be responsible for more than 50% of the mortalities, majority of which consist of coronary artery diseases.[1,2]

Diabetes is a metabolic disease accompanied with hyperglycemia, with an increasing incidence rate. Cardiovascular diseases may cause macro- and micro-complications, such as retinopathy, neuropathy, and nephropathy. Diabetes is a significant and independent risk factor for cardiovascular morbidity and mortality. The clinical course of diabetes is determined by both genetic and environmental factors, and can appear as hyperinsulinemia and insulin resistance, starting off as pancreatic β-cell dysfunction years before diabetes develops.[3,4] Therefore, it is important to screen the individual in the high-risk group to administer appropriate diagnostic tests, and to take timely precautions to prevent diabetic macro- and micro-complications.

Many studies are available in the medical literature explaining the effects of using different types of dialysis membranes on insulin filtration and sensitivity among diabetic patients on hemodialysis (HD) treatment due to end-stage renal failure (ESRF). For example, Abe et al. have reported that using different types of high-flux dialysis membranes impact insulin filtration in different ways among type-2 diabetes patients with ESRF, who are on insulin therapy.[5,6] However, as insulin resistance is proved to be increased in ESRF patients in prior studies, there are limited number of studies that demonstrate the effect of using different dialysis membranes on insulin sensitivity and resistance in non-diabetic ESRF patients. In this study, we aimed to investigate the effects of polysulfone (PS) and ''polyarylethersulfone, polyvinylpyrrolidone, polyamide (PPP)'' membranes on insulin resistance in non-diabetic ESRF patients.

Materials and methods

This study was conducted on 46 patients (21 females, 25 males) receiving HD therapy regularly due to ESRF. None of the cases had residual renal function. Mean duration of HD was 78.72 ± 29 months. All participants were above 18 years of age (mean ± standard deviation (SD): 61.90 ± 11 years), none of them had diabetes mellitus at the time of enrollment, and their fasting blood glucose was <126 mg/dl. PS

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Table 1. Patient characteristics.

Age	61.90 ± 11
Female/male	21/25
Duration of dialysis (months)	78.72 ± 29
Body mass index (kg/m^2)	24.2 ± 4.6
Creatinine (mg/dl)	7.87 ± 1.1
Parathyroid hormone (pg/mL)	301.230 ± 101
Calcium (mg/dl)	8.61 ± 1.2
Phosphorus (mg/dl)	5.252 ± 1.3
Uric acid (mg/dl)	6.352 ± 1.4
Albumin (g/dl)	3.80 ± 0.40
Hemoglobin (g/dl)	10.9 ± 0.80

membrane was used for HD for the past 1 year. Patients with diabetes, obesity, and hyperlipidemia and those on medications such as corticosteroid that can affect the insulin level were excluded from the study. At the initiation of the study, the mean (SD) values were as follows – body mass index (BMI): 24.2 ± 4.6 kg/m^2; creatinine: 7.87 ± 1.1 mg/dl; parathormone (PTH): 301.230 ± 101 pg/mL; calcium (Ca): 8.61 ± 1.2 mg/dl, phosphorus (P): 5.252 ± 1.3 mg/dl; uric acid: 6.352 ± 1.4 mg/dl; albumin: 3.80 ± 0.40 g/dl, and hemoglobin: 10.9 ± 0.80 g/dl (Table 1). All patients received a 35 Cal/kg/day diet, including 1.2 g/kg/day of protein, 1600 mg/day of Ca, and 600 mg/day of P. Their ongoing medical treatments were not altered throughout the study.

All patients received a 4-hour HD treatment 3 times a week with blood flow rate of 300 mL/min. The dialysate temperature was 37°C. All patients were administered 2600–4000 units of heparin as an anticoagulant. The surface area of the two different membranes [PS (Rexeed-SX, Ashai Kasei Medical, Memphis, TN) and PPP (Polyflux-H, Gambro AB, Lund, Sweden)] used in the study was 1.5 m^2. The fractioned urea clearance (*Kt*/*V*) was assessed for each case by calculating the clearance of the dialysis membrane, duration of dialysis, urea reduction ratio, and the volume of distribution of urea based on Cogan and Garovoy's linear regression graph. In order to rule out the abnormal results in volume changes, the urea distribution volume of each patient was recalculated using Watson's anthropometric equation and the cases with deviations greater than 10% in comparison to the urokinetic model were excluded from the study.

Prior to the study, pre-dialysis blood was drawn from all patients in the morning, following an average of 10-hour fasting. Blood glucose, insulin, PTH, Ca, and P values were measured. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) (Glucose × Insulin × 0.05551/22.5) was calculated based on fasting glucose and insulin values. The PS dialysis membrane, used by all patients previously was replaced with PPP high-flux membrane that has the same surface area over 12 weeks. Their pump rates were kept constant throughout the study and at the end of the 12-week period, HOMA and *Kt*/*V* values were recalculated and compared.

The results are expressed as mean ± SD or as counts. The normality of each variable's distribution was investigated with the Kolmogorov–Smirnov test. For between-group comparisons, Student's *t*-test was used for variables with normal distribution and the Mann–Whitney *U*-test for variables with non-normal distribution. *p*-Values <0.05 were considered statistically significant. SPSS 20.0 software (Chicago, IL) was used for statistical analyses.

Table 2. The biochemical difference between PS and PPP treatments.

	PS	PPP	*p*
Glucose (mg/dl)	97.52 ± 2.183	92.32 ± 2.229	0.006
Insulin (μU/mL)	15.780 ± 1.8132	13.209 ± 1.6665	0.084
HOMA-IR	3.268 ± 0.4643	2.926 ± 0.4476	0.850
Kt/*V*	1.575 ± 0.535	1.753 ± 0.398	0.002

Notes: PS: Polysulfone; PPP: Polyarylethersulfone, polyvinylpyrrolidone, polyamide; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance; *Kt*/*V*: dialysis efficiency value.

Results

All patients completed the study ($n = 46$). As displayed in Table 2, the mean *Kt*/*V* value obtained with PS membrane was 1.575 and with PPP membrane at the end of 12 weeks was 1.753, and the difference was statistically significant ($p = 0.002$). Comparison of the HOMA-IR values showed that it was lower with the PPP membrane (2.926) than with the PS membrane (3.268), but the difference could not reach the level of statistical significance ($p = 0.085$). The mean fasting blood glucose values with PS and PPP membranes were 97.52 and 92.22 mg/dl, respectively, and the difference was found statistically significant ($p = 0.006$). The mean insulin value was 15.780 μU/mL with the PS membrane and 13.209 μU/mL with the PPP membrane, and their comparison did not yield a statistically significant difference ($p = 0.084$).

Discussion

Our study findings show that, HD treatment using PPP high-flux membrane provides a more effective dialysis and has more positive effect on glucose metabolism, compared to those using PS membrane. Studies discussing the effect of different high-flux dialysis membranes on the insulin clearance of type-2 diabetes patients are available in the medical literature. For example, Abe et al. have shown that three different types of high-flux HD membranes have different HD clearance values.[5–8] However, the studies demonstrating their effects on insulin clearance and resistance of non-type-2 diabetic ESRF patients are limited in the medical literature. We could not encounter a study in the medical literature that compares the effects of using PPP or PS membranes among non-diabetic ESRF patients on their endogenous insulin clearance and resistance. Our findings suggest that HD administered via PPP high-flux membrane significantly increases *Kt*/*V* values compared to the PS membrane, and causes a slight decrease in HOMA-IR value, though not significantly. The difference in the results obtained despite the high-flux nature of both the membranes and similar pump rate and surface area, made us conclude that the high-flux membranes having different structures impacted the efficiency of dialysis, insulin clearance, and insulin sensitivity.

Numerous parameters are used to confirm the dialysis is administered objectively. The leading among these is fractioned urea clearance, calculated as *Kt*/*V* value, which shows the efficiency of the dialysis.[9,10] Having a *Kt*/*V* value of at least 1.2 has been reported as a factor that reduces morbidity and mortality. Our findings suggest that the *Kt*/*V* values among patients using PPP membrane are significantly higher than those using PS membrane, which led us to conclude that

the PPP membrane provides a more effective dialysis than the PS membrane.

Uremia developed in ESRF may cause various impairments in carbohydrate metabolism, such as glucose intolerance, reduced insulin sensitivity, and insulin resistance.[11–14] Insulin resistance in ESRF is believed to be due to certain uremic toxins supported by the reduction in insulin resistance via HD. On another note, the insulin resistance in ESRF is also believed to be influenced by factors such as metabolic acidosis, hyperparathyroidism, and anemia.[15–18] In chronic renal failure, insulin that circulates in the blood stream increases, insulin resistance develops, use of glucose in the peripheral tissues and insulin secretion is impaired as the insulin response of pancreas to hyperglycemia is reduced. Therefore, an effective dialysis in ESRF will lead to increased *Kt*/*V* values, and the removal of uremic toxins from the blood as a result of effective dialysis will reduce insulin resistance, leading to increased insulin sensitivity and glucose use in peripheral tissues, thus reducing glucose and insulin levels along with lowered HOMA-IR values.[13,14,16] According to our findings, *Kt*/*V* value was significantly increased by the PPP membrane compared to the PS membrane, which proves that PPP membrane provides a more effective dialysis. Additionally, though it did not reach a level of significance, use of PPP membrane also slightly reduced HOMA values, increased insulin sensitivity, and reduced insulin resistance compared to the PS membrane. The mean HD duration in our PS patients was 12 months. The results obtained by the end of 12 weeks are the changes demonstrated due to the use of PPP membrane. Therefore, the changes in *Kt*/*V* and HOMA-IR values may be expected to be more prominent as the duration of PPP membrane increases. We also believe that increased sample size and conduction of new similar studies will further clarify the results.

Reduced plasma glucose due to endogenous insulin clearance is expected following an effective HD. Based on our results, insulin levels were lower, though not significantly, while glucose levels were significantly lower and *Kt*/*V* was significantly higher with the PPP membrane compared to the PS membrane. These data suggest a more effective dialysis and reduced glucose levels. The fact that glucose levels were significantly lower with the use of PPP membrane compared to the PS membrane, suggested that reduced glucose levels might be the result of better filtration due to membrane characteristics.

Insulin resistance is known as a cardiovascular risk factor.[19–21] Studies showed that high-flux membranes are better than low-flux membranes in terms of reducing insulin resistance and cardiovascular mortality and morbidity.[22–24] With recent developments in dialysis technology, the inflammation caused by HD is observed less frequently with biologically adaptive membranes; uremic toxins, medium and large molecules are better cleaned; and hyperlipidemia and oxidative stress are observed less frequently. Therefore, high-flux membranes have better clinical outcomes, and hence, are specifically preferred.[23–26] On the other hand, effects of different high-flux membranes on insulin resistance are not known. Different types of synthetic high-flux membranes have difference performances. Since insulin resistance is a cardiovascular risk factor affecting mortality and morbidity, membranes reducing this risk can further reduce cardiovascular mortality and morbidity, as well. In our study, PPP membrane provided a more effective dialysis and lower insulin resistance compared to the PS membrane. Still, there is a need for further studies to be conducted over longer period of time on this topic.

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The study protocol was approved by the Ethics Committee of Cerrahpaşa Medical School, Istanbul University, Istanbul.

Declaration of interest

The authors declare no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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