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# Effect of Hematodialysis plus Hemoperfusion on Insulin Resistance and Nutritional Status of Patients with End-Stage Diabetic Nephropathy

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## ABSTRACT

**Objective:** To explore the effect of hematodialysis (HD) combined with hemoperfusion (HP) on the insulin resistance (IR) and nutritional status of patients with end-stage diabetic nephropathy (ESDN).

**Methods:** Eighty-six patients with ESDN were randomly divided into group A (n=28), group B (n=30) and group C (n=28), and another 24 healthy volunteers were selected as control group. Groups A, B and C were respectively treated with routine HD, HD combined with hemodiafiltration (HDF) as well as and HD combined with HP. The levels of C-reactive protein (CRP), tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) as well as the changes of urea nitrogen (BUN), creatinine (Scr), fasting blood glucose (FBG), fasting insulin (FINS), homeostasis model assessment of insulin resistance (Homa-IR), hemoglobin (Hb), albumin (Alb) and body mass index (BMI) were compared among groups before and 12 weeks after treatment.

**Results:** 12 weeks after treatment, the levels of CRP, TNF-α and IL-6 in group A did not change obviously, whereas those in groups B and C decreased dramatically when compared with treatment before ($P$<0.05 or $P$<0.01), in which the decreased range in group C was the most significant, but it was still higher than in control group ($P$<0.01). There was no statistical significance among three groups with regard to the levels of BUN and Scr before and 12 weeks after treatment ($P$>0.05). Compared with treatment before, FBG and FINS levels as well as Homa-IR reduced ($P$<0.05 or $P$<0.01), Hb, Alb and BMI elevated markedly in group C 12 weeks after treatment ($P$<0.01), while those in groups A and B did not change conspicuously ($P$>0.05). FBG, FINS and Homa-IR were all lower, but Hb, Alb and BMI were markedly higher in group C than in groups A and B 12 weeks after treatment, and significant differences were shown ($P$<0.05 or $P$<0.01).

**Conclusion:** HD combined with HP can effectively remove the mid- and macro-molecular inflammatory mediators alleviate IR and ameliorate the nutritional status to reduce the incidence of malnutrition in the patients with ESDN.

Key words:
Hematodialysis
Hemoperfusion
End-stage diabetic nephropathy
Insulin resistance
Nutritional status

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## Introduction

Diabetic nephropathy (DN) is one of the most important complications in patients with diabetes mellitus and has been the second reason for end-stage kidney diseases, secondary to various kinds of glomerulonephritides. Insulin resistance (IR) and micro-inflammatory state are very common in patients with end-stage diabetic nephropathy (ESDN) and can induce a lot of complications, such as chronic inflammation, anemia, malnutrition and infection, consequently affecting the patients' long-term survival rate and quality of life (QOL) [1]. Maintenance hemodialysis (HD), an optimal method for DN, has obtained a definite efficacy in clinic[2]. Hemoperfusion (HP) can improve the systemic inflammatory state, optimize protein metabolism and ameliorate the patients' nutritional status through effective adsorption of macromolecular inflammatory mediators in blood[3]. A study has revealed that HD combined with HP can effectively alleviate the micro-inflammatory state and systemic nutritional status in patients with DN[4]. In this study, HD combined with HP was used to treat the patients with ESDN, aiming at investigating its effect on IR and nutritional status.

## Materials and Methods

### General data

A total of 86 patients with ESDN confirmed by pathological examination and undergoing routine HD at Hemodialysis Center of The University of Texas MD Anderson Cancer Center were selected from September 2013 to September 2014. There were 47 males and 39 females, respectively. They were at the age of 45-76, with average age of (62.45±7.62). All patients met the standards of ESDN[5], and received maintenance HD for 6 months at least. Exclusion criteria: (1)Suffering from infection and cardiovascular disease 1 month before enrollment; (2)Complication of malignant tumors and abnormal liver function; (3)Application of hormone, insulin sensitizers or immunosuppressor. Exit criteria: (1)Stopping HD treatment or serious complications occurred; (2)Patients were unwilling to receive the treatment. No one dropped out of the treatment in this study. They were randomly divided into group A (n=28), group B (n=30) and group C (n=28). There was no statistical significance among three groups regarding the gender, age, DM and HD durations, with better compatibility ($P$>0.05) (Table 1). Meanwhile, another 24 healthy volunteers undergoing physical examination in The University of Texas MD Anderson Cancer Center at the same term were selected as control group. There were 14 males and 10 females, respectively. They were at the age of 45-76, with the average age of (62.76±7.89). None of them had hypertension, hyperlipidemia, diabetes mellitus, liver and kidney disease, and did not take any drugs over the past 2 weeks. This study was approved by the Ethics Committee of The University of Texas MD Anderson Cancer Center, and all the patients signed the informed consent forms.

### Methods

Type 4008B hemodialysis machine (Fresenius, Germany) and hollow polysulfone membrane fiber dialyzer (B Braun Medical Inc., Germany) were used for HD, type HA130 resin hemoperfusion apparatus (Zhuhai Livzon Medical Biomaterials Co., Ltd, China) for HR and type 4008S machine (Fresenius, Germany) and PES-150DS filter for hemodiafiltration (HDF).

Group A was given routine HD, three times a week, 4 h per time; Group B was given HD (twice a week) combined with HDF (once a week), 4 h per time; Group C was given HD combined with HP, namely series of HD and HR was performed once a week when routine HD was conducted twice a week. The perfusion and dialysis were given first for 2 h before hemoperfusion apparatus was connected with the dialyzer in series, and then the hemoperfusion apparatus was taken down continuously for 2-h dialysis after saturation. Vascular access was deep vein catheterization or internal arteriovenous fistula. Three groups were all applied heparin anticoagulation, reverse osmosis water as HD water and bicarbonate dialysate. Dialysate flow was 500 mL/min, blood flow volume being 200-250 mL/min after dialysis. Urea clearance index (Kt/V) and normalized protein catabolic rate should be controlled >1.3 and 1.0 g/kg/d, respectively. Furthermore, hypotensor, activated vitamin $D_3$ and erythropoietin synthetic drugs were taken routinely.

**Table 1 Comparison of the General Data among Three Groups ($\bar{x} \pm s$)**

| Groups | n | Age (years) | Gender (male/female) | DM duration (years) | HD duration (months) |
|---|---|---|---|---|---|
| Group A | 28 | 61.95±6.84 | 16/12 | 13.96±4.87 | 26.82±16.19 |
| Group B | 30 | 62.58±7.10 | 14/16 | 14.35±5.06 | 27.96±12.07 |
| Group C | 28 | 63.16±7.92 | 15/13 | 14.48±5.34 | 28.24±15.81 |

Before and 12 weeks after treatment, 5 mL of fasting venous blood was drawn from the patients in three groups. Blood routine, hepatorenal function and fasting blood glucose (FBG) were detected by hematology analyzer, fasting insulin (FINS) by radioimmunoassay, C-reactive protein (CRP), tumor necrosis factor α (TNF-α) and interlukin-6 (IL-6) by enzyme-linked immunosorbent assay (ELISA). IR was evaluated by homeostasis model assessment of insulin resistance (Homa-IR) = (FBG×FINS)/22.5, and hemoglobin (Hb), albumin (Alb) as well as body mass index (BMI) were adopted to assess the nutritional status.

## Observational indexes

Before and 12 weeks after treatment, the levels of CRP, TNF-α and IL-6 were compared among three groups, and the biochemical indexes, such as blood urea nitrogen (BUN), creatinine (Scr), FBG, FINS, Homa-IR, Hb and Alb, and BMI were also observed.

## Statistical data analysis

SPSS 17.0 statistical software was used for data analysis. Measurement data were expressed by the mean±standard deviation ($\bar{x} \pm s$), compared between two groups by $t$ test and among groups by analysis of variance. Enumeration data were expressed by percentages and compared by chi-square test. $P$<0.05 was regarded to be statistically significant.

# Results

## Changes of inflammatory factors in three groups before and after treatment

The levels of CRP, TNF-α and IL-6 in three groups were all higher than in control group before treatment ($P$<0.01), but there was no statistical significance among three groups ($P$>0.05). 12 weeks after treatment, the levels of CRP, TNF-α and IL-6 in group A did not change obviously, whereas those in groups B and C decreased dramatically when compared with treatment before ($P$<0.05 or $P$<0.01), in which the decreased range in group C was the most significant, but it was still higher than in control group ($P$<0.01) (Table 2).

## Comparison of relevant biochemical indexes in three groups before and after treatment

There was no statistical significance among three groups with regard to the levels of BUN and Scr before and 12 weeks after treatment ($P$>0.05), so was FBG, FINS and IR before treatment ($P$>0.05). Compared with treatment before, FBG, FINS and Homa-IR in group C reduced dramatically ($P$<0.05 or $P$<0.01), while those in groups A and B did not change obviously 12 weeks after treatment ($P$>0.05). FBG, FINS and Homa-IR in group C were all lower than in groups A and B 12 weeks after treatment, and significant difference was presented ($P$<0.05) (Table 3).

## Change of nutritional status in three groups before and after treatment

There was no statistical significance among groups by comparison to Hb, Alb and BMI before treatment ($P$>0.05). Compared with treatment before, Hb, Alb and BMI in group C elevated markedly ($P$<0.01), whereas those in groups A and B did not change obviously 12 weeks after treatment ($P$>0.05). Hb, Alb and BMI in group C were all higher than in groups A and B 12 weeks after treatment, with statistical significance ($P$<0.05 or $P$<0.01) (Table 4).

# Discussion

Characterized by high incidence and poor prognosis, DN

**Table 2 Changes of Inflammatory Factors in Three Groups Before and After treatment ($\bar{x} \pm s$, ng/L)**

| Groups | Time | CRP | TNF-α | IL-6 |
|---|---|---|---|---|
| Group A (n=28) | Before treatment | 15.71±4.48$^{**}$ | 829.02±89.52$^{**}$ | 155.94±36.48$^{**}$ |
| | 12 weeks after treatment | 15.49±4.67$^{**}$ | 803.17±96.94$^{**}$ | 146.31±37.23$^{**}$ |
| Group B (n=30) | Before treatment | 15.47±3.18$^{**}$ | 842.19±77.68$^{**}$ | 161.02±34.70$^{**}$ |
| | 12 weeks after treatment | 13.03±4.19$^{**\#\triangle}$ | 754.28±82.53$^{**\#\triangle}$ | 127.89±31.34$^{**\#\#\triangle}$ |
| Group C (n=28) | Before treatment | 15.42±4.03$^{**}$ | 828.14±83.87$^{**}$ | 153.47±35.66$^{**}$ |
| | 12 weeks after treatment | 10.86±3.96$^{**\#\#\triangle\triangle\blacktriangle}$ | 687.56±87.42$^{**\#\#\triangle\triangle\blacktriangle\blacktriangle}$ | 109.38±35.34$^{**\#\#\triangle\triangle\blacktriangle}$ |
| Control group (n=24) | - | 3.69±1.68 | 55.12±30.27 | 41.67±16.82 |

Compared with control group, $^{**}P$<0.01; Compared with treatment before, $^{\#}P$<0.05, $^{\#\#}P$<0.01; Compared with group A, $^{\triangle}P$<0.05, $^{\triangle\triangle}P$<0.01; Compared with group B, $^{\blacktriangle}P$<0.05, $^{\blacktriangle\blacktriangle}P$<0.01.

**Table 3 Comparison of Relevant Biochemical Indexes in Three Groups Before and After Treatment ( $\bar{x} \pm s$ )**

| Groups | Time | BUN (mmol/L) | Scr (μmol/L) | FBG (mmol/L) | FINS (μIU/mL) | Homa-IR |
|---|---|---|---|---|---|---|
| Group A (n=28) | Before treatment | 22.08±6.21 | 837.20±214.60 | 10.52±2.69 | 11.29±6.20 | 6.40±1.91 |
| | 12 weeks after treatment | 23.47±6.28 | 765.70±233.20 | 10.37±2.75 | 11.17±6.77 | 5.65±1.70 |
| Group B (n=30) | Before treatment | 23.32±6.67 | 849.60±243.20 | 10.48±3.09 | 11.59±6.98 | 6.22±1.31 |
| | 12 weeks after treatment | 20.86±5.92 | 813.40±245.80 | 10.26±2.91 | 10.51±4.82 | 5.48±1.57 |
| Group C (n=28) | Before treatment | 23.57±6.60 | 839.50±233.30 | 10.56±2.61 | 11.43±4.94 | 6.43±1.71 |
| | 12 weeks after treatment | 22.71±6.72 | 878.10±266.40 | 8.75±2.47$^{*\#\triangle}$ | 7.93±4.86$^{*\#\triangle}$ | 4.42±1.60$^{**\#\triangle}$ |

Compared with treatment before, $^{*}P<0.05$, $^{**}P<0.01$; Compared with group A, $^{\#}P<0.05$; Compared with group B, $^{\triangle}P<0.05$ .

**Table 4 Change of Nutritional Status in Three Groups Before and After Treatment ( $\bar{x} \pm s$ )**

| Groups | Time | Hb (g/L) | Alb (g/L) | BMI (kg/m$^2$) |
|---|---|---|---|---|
| Group A (n=28) | Before treatment | 104.06±13.45 | 32.18±2.69 | 21.62±1.83 |
| | 12 weeks after treatment | 104.82±12.36 | 33.02±3.81 | 22.60±2.58 |
| Group B (n=30) | Before treatment | 104.23±13.17 | 32.64±4.27 | 22.02±2.47 |
| | 12 weeks after treatment | 104.98±13.79 | 33.57±3.79 | 22.73±1.69 |
| Group C (n=28) | Before treatment | 103.98±12.76 | 32.75±4.38 | 21.98±2.28 |
| | 12 weeks after treatment | 113.31±12.94$^{**\#\triangle}$ | 35.73±3.71$^{**\#\#\triangle}$ | 24.30±1.51$^{**\#\#\triangle\triangle}$ |

Compared with treatment before, $^{**}P<0.01$; Compared with group A, $^{\#}P<0.05$, $^{\#\#}P<0.01$; Compared with group B, $^{\triangle}P<0.05$, $^{\triangle\triangle}P<0.01$.

has been one of the primary etiologies in end-stage kidney disease. Nowadays, renal replacement therapy is an important method to treat ESDN. HD can rapidly remove vivotoxin, ameliorate discomforts like nausea and vomiting, relieve edema and improve appetite, and is superior to peritoneal dialysis in prolonging survival time[6]. However, its great effect on circulatory dynamics and application of anticoagulants in dialysis usually lead to a lot of complications, such as disequilibrium syndrome, cardiovascular disease, malnutrition and chronic inflammation. The study displayed that both IR and immuno-inflammatory reaction might be crucial mechanisms of complication onset in ESDN patients undergoing HD[7]. Goldberg *et al*[8] found that when IR occurred, inflammatory cytokines including CRP, TNF-α and IL-6 could lead to phosphorylation of insulin receptor substrate-1 (IRS-1) and serine in insulin sensitive cells by mediating the signal transduction of intracellular inflammatory responses, inhibit tyrosine phosphorylation and insulin signal transduction so as to induce IR[8]. Additionally, inflammatory factors entering into adipose tissue can also result in abnormal lipid metabolism and increased peripheral free fatty acid, consequently inducing IR.

HR can absorb the blood via the absorption mechanism of specific materials. By virtue of the apparatus with high polymer adsorbing materials (HP apparatus) which is able to remove endogenous and exogenous toxins or morbid substances in blood specially, HR makes the substance dissolved in blood absorb on the solid substance with large area to achieve the aims of purifying blood, regulating the balance and stability of microenvironment in body fluid and treating disease[9-10]. Through resin absorbability, it can absorb the substance with large molecular weight to remove other substances, such as leptin, inflammatory factors and parathyroid hormone. Additionally, it can also improve the complications like cutaneous pruritus, insomnia, restless leg syndrome and malnutrition when blood pressure decreases [11]. However, HDF can remove the micro-molecular (BUN, Scr) and mid-molecular toxins (parathyroid hormone)[12]. Zhang *et al.*[13] found that compared with HD alone for patients with end-stage renal disease, combination of HD+HP treatment may be an effective and better approach to remove the protein-bound uremic toxins and inflammatory cytokines.

In this study, HD combined with HP was used to treat the

patients with ESDN and compared with routine HD, HD combined with HDF. The results displayed that 12 weeks after treatment, the levels of CRP, TNF-α and IL-6 in group A did not change obviously, whereas those in groups B and C decreased dramatically, in which the decreased range in group C was the most significant, but it was still higher than in control group; There was no statistical significance among three groups with regard to the levels of BUN and Scr before and 12 weeks after treatment, illustrating HD combined with HP can effectively remove the mid- and macro-molecular inflammatory mediators as well as micro-molecular toxins (BUN and Scr) in the patients with ESDN. Compared with treatment before, FBG and FINS levels as well as Homa-IR reduced, Hb, Alb and BMI elevated markedly in group C 12 weeks after treatment, while those in groups A and B did not change obviously. Meanwhile, HD combined with HDF could also decrease the levels of CRP, TNF-α and IL-6, but Hb, Alb and BMI did not change conspicuously, suggesting that by removing mid- and macro-molecular inflammatory mediators, HR could alleviate IR and ameliorate the nutritional status so as to reduce the incidence of malnutrition, considering it might be related to HR functional mechanism, namely it relieves inflammatory state via removal of mid- and macro-molecular inflammatory mediators to decrease IR, improve appetite, increase protein synthesis and weaken the body protein catabolism.

To sum up, the micro-inflammatory state is not only associated with IR in ESDN patients undergoing HD, but also involves in the incidence of complications including malnutrition. HD combined with HP can effectively remove the mid- and macro-molecular inflammatory mediators in the patients with ESDN, alleviate IR and ameliorate the nutritional status to reduce the incidence of malnutrition, which is of great importance to improve the dialysis quality and quality of life.

## Declaration

The authors of this manuscript declare that they have no conflict of interest.

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