SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 DOI: 10.5937/jomb0-63909

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 45: 1–10, 2026 *Original paper*
Originalni naučni rad

IMPACT OF HEMODIALYSIS COMBINED WITH HEMOPERFUSION ON METABOLISM, CYTOKINES, AND NOVEL BIOMARKERS IN CHRONIC KIDNEY DISEASE PATIENTS

UTICAJ HEMODIJALIZE U KOMBINACIJI SA HEMOPERFUZIJOM NA METABOLIZAM, CITOKINE I NOVI BIOMARKERI KOD PACIJENATA SA HRONIČNOM BOLEŠĆU BUBREGA

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Summary

Background: Chronic kidney disease (CKD) often progresses to end-stage renal disease (ESRD), severely affecting patients' lives. This article explored the effects of hemodialysis (HD) combined with hemoperfusion (HP) on metabolic indicators, inflammatory cytokines, and novel biomarkers – including oxidative stress markers (malondialdehyde, MDA; superoxide dismutase, SOD), vascular endothelial markers (endothelin-1, ET-1), fibrosis markers (transforming growth factor-beta1, TGF-β1), and metabolic risk markers (homocysteine, Hcy) – in CKD patients. **Methods:** A retrospective analysis was conducted on clinical data from 72 CKD patients admitted to Changxing County Hospital of Traditional Chinese Medicine from October 2023 to October 2025. Patients were divided into the HD+HP group (AG, n=35) and the HD group (BG, n=37). Changes in metabolic indicators, inflammatory factors, and novel biomarkers were compared before and after 6 months of treatment. **Results:** After treatment, the AG showed markedly lower levels of BUN, Scr, iPTH, and β_2-MG compared to the BG ($P<0.05$), with a 42.3% reduction in iPTH (326.7±58.4 pg/mL vs. 566.2±89.1 pg/mL). The AG also had markedly lower levels of IL-6, TNF-α, and hs-CRP ($P<0.01$). Novel biomarkers, including MDA, ET-1, TGF-β1, and Hcy, were significantly lower in AG post-treatment ($P<0.05$), while SOD activity was significantly increased. No visible distinction was noted in adverse event rates ($P>0.05$). **Conclusion:** HD combined with HP can more effectively remove medium- and large-molecular-weight toxins, im-

Kratak sadržaj

Uvod: Hronična bubrežna bolest (HBB) često napreduje do terminalne bubrežne insuficijencije (ESRD), što ozbiljno utiče na kvalitet života pacijenata. Ovaj rad je ispitivao efekte hemodijalize (HD) u kombinaciji sa hemoperfuzijom (HP) na metaboličke pokazatelje, inflamatorne citokine i nove biomarkere, uključujući markere oksidativnog stresa (malondialdehid, MDA; superoksid-dizmutaza, SOD), markere vaskularnog endotela (endotelin-1, ET-1), markere fibroze (transformišući faktor rasta beta-1, TGF-β1) i metaboličke markere rizika (homocistein, Hcy) – kod pacijenata sa HBB.
Metode: Sprovedena je retrospektivna analiza kliničkih podataka kod 72 pacijenta sa HBB lečenja u Okružnoj bolnici tradicionalne kineske medicine u čangšingu u periodu od oktobra 2023. do oktobra 2025. godine. Pacijenti su podeljeni u grupu HD+HP (AG, n=35) i grupu HD (BG, n=37). Promene metaboličkih pokazatelja, inflamatornih faktora i novih biomarkera upoređene su pre i nakon 6 meseci lečenja.
Rezultati: Nakon lečenja, u AG su zabeleženi značajno niži nivoi BUN, Scr, iPTH i β_2-MG u poređenju sa BG ($P<0,05$), uz smanjenje iPTH od 42,3% (326,7±58,4 pg/mL naspram 566,2±89,1 pg/mL). AG je takođe imala značajno niže nivoe IL-6, TNF-α i hs-CRP ($P<0,01$). Novi biomarkeri, uključujući MDA, ET-1, TGF-β1 i Hcy, bili su značajno niži u AG nakon terapije ($P<0,05$), dok je aktivnost SOD bila značajno povećana. Nije uočena značajna razlika u učestalosti neželjenih događaja između grupa ($P>0,05$).

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prove oxidative stress, endothelial function, and fibrosis markers, and markedly improve calcium-phosphorus metabolism disorders and micro-inflammatory status, providing comprehensive clinical evidence for optimizing blood purification strategies.

Keywords: HD, HP, CKD, metabolism, cytokines, oxidative stress, endothelial dysfunction, fibrosis, homocysteine, biomarkers

Zaključak: Hemodijaliza u kombinaciji sa hemoperfuzijom efikasnije uklanja toksine srednje i velike molekulske mase, poboljšava oksidativni stres, funkciju endotela i markere fibroze, kao i poremećaje metabolizma kalcijuma i fosfora i mikroinflamatorni status, čime pruža sveobuhvatne kliničke dokaze za optimizaciju strategija prečišć avanja krvi.

Ključne reči: HD, HP, HBB, metabolizam, citokini, oksidativni stres, endotelna disfunkcija, fibroza, homocistein, biomarkeri

Introduction

Chronic kidney disease (CKD) is a major global public health issue with rising incidence, often progressing to end-stage renal disease (ESRD), requiring renal replacement therapy for survival (1, 2). Hemodialysis (HD) is the most commonly used treatment for patients with ESRD. However, traditional HD has limited efficacy in removing medium- and large-molecular-weight toxins (e.g., β_2-MG, iPTH) and inflammation-related cytokines (3, 4). The accumulation of these toxins is closely related to complications in CKD patients, severely affecting their quality of life and prognosis.

HD, one of the main renal replacement therapies for end-stage CKD patients (5), can effectively remove small-molecular toxins such as urea and creatinine by diffusion, playing a crucial role in maintaining patients' lives and delaying disease progression (6, 7). However, HD has a limited ability to remove medium- and large-molecular-weight toxins, such as iPTH and β_2-MG, and it is difficult to improve the chronic inflammatory state in patients markedly. Studies have shown that long-term accumulation of iPTH and β_2-MG is closely related to serious complications such as renal osteodystrophy and dialysis-related amyloidosis (8). Increased levels of inflammatory factors not only exacerbate metabolic disorders but are also closely linked to the occurrence and development of cardiovascular diseases, becoming a key factor affecting the prognosis of CKD patients (9, 10).

Beyond traditional metabolic and inflammatory markers, emerging biomarkers such as oxidative stress indicators (MDA, SOD), endothelial dysfunction markers (ET-1), fibrosis mediators (TGF-β1), and metabolic risk factors (Hcy) have gained attention for their roles in CKD progression and cardiovascular complications. These biomarkers reflect underlying pathophysiological processes, including oxidative damage, vascular injury, tissue fibrosis, and accelerated atherosclerosis, which conventional HD does not adequately address.

Hemoperfusion (HP) is a treatment that removes endogenous and exogenous toxins from the blood using adsorbents, effectively clearing large molecular and protein-bound toxins, compensating for the shortcomings of HD (11). The combination of HD and HP can theoretically achieve synergistic removal of small, medium, and large molecular toxins, effectively intervene in inflammatory factors, improve patients' metabolic status, and reduce systemic inflammatory responses (12). Although HD+HP therapy has been gradually adopted in clinical practice, studies on its impact on metabolic indicators, cytokines, and novel biomarkers in CKD patients remain limited. Most studies focus on single indicators, have small sample sizes ($n<50$), short observation periods ($\leq$3 months), and lack a systematic assessment of the metabolic-inflammatory-oxidative network linkage (13, 14).

This article retrospectively analyzed clinical data from 72 CKD patients, synchronously monitoring changes in metabolic profiles [BUN/Scr (small molecules), iPTH/β_2-MG (medium and large molecules)], inflammatory profiles [IL-6/TNF-α (cytokines), hs-CRP (acute-phase protein)], and novel biomarker profiles [oxidative stress (MDA, SOD), endothelial function (ET-1), fibrosis (TGF-β1), and metabolic risk (Hcy)]. It clarified the regulatory effects of HD+HP therapy on metabolic balance, microinflammatory status, and multisystem pathophysiological pathways, providing comprehensive, evidence-based support for optimizing blood purification strategies.

Materials and Methods

Subjects

Clinical data of 72 CKD patients admitted to Changxing County Hospital of Traditional Chinese Medicine from October 2023 to October 2025 were retrospectively analyzed. Patients were divided into AG (HD+HP, n=35) and BG (HD only, n=37). The AG comprised 17 men and 18 women, aged 25–61 years (mean 47.86±3.51), with BMI 26–34 kg/m^2 and disease duration 3.62±4.21 years. The BG included 23 men and 14 women, aged 27–62 years (mean 46.84±2.17), with BMI 26–34 kg/m^2 and disease duration 3.58±3.82 years. Clinical data of

the subjects were comparable ($P>0.05$). Informed consent was obtained from all subjects. The study received ethical approval from the Ethics Committee of Changxing County Hospital of Traditional Chinese Medicine.

Inclusion criteria

1. Individuals meeting CKD diagnostic criteria in the *Clinical Practice Guidelines for CKD* (15), confirmed by laboratory tests and clinical symptoms, and requiring renal replacement therapy;
2. KDIGO 2012 CKD diagnostic criteria (16);
3. Serum iPTH>300 pg/mL or β_2-MG>25 mg/L;
4. Regular HD treatment >3 months (3 times/week, 4 h each);
5. Patients and legal guardians agreed to participate and signed consent forms.

Exclusion criteria

1. Severe psychological disorders or intellectual disabilities affecting understanding and cooperation;
2. Contraindications such as severe coagulation dysfunction, allergy to dialysis membrane or adsorbent, or inability to establish vascular access;
3. Pregnant or breastfeeding women;
4. Severe liver dysfunction (Child-Pugh Class C);
5. Incomplete clinical data;
6. Mental abnormalities affecting normal communication.

Methods

All patients received conventional treatment, including blood glucose control, maintenance of electrolyte balance, correction of anemia, and regulation of blood pressure.

HD-only group (BG)

Patients received HD only, using an FX10 hollow-fiber dialyzer (Fresenius, Germany) and an RO-JS280C water treatment system (Beijing Mailing Medical Technology Development Co., Ltd.). Bicarbonate dialysate was used, with blood flow of 200–250 mL/min and dialysate flow of 500 mL/min. HD was performed 3 times/week for 4 h each session for 6 months. Vital signs and dialysis parameters were closely monitored. Anticoagulants were selected based on coagulation function and individual differences.

HD+HP group (AG)

Patients received HD plus HP, using a YTS-60 perfusion device (Zibo Kangbei Medical Device Co., Ltd.). The perfusion device was connected in series with the dialyzer. HP was performed for 2 h followed by HD for 2 h. Blood flow was 200–250 mL/min, and dialysate flow was 500 mL/min. Treatment was performed 2 times/week for 4 h each time for 6 months. Vital signs, blood flow, and dialysate parameters were closely monitored. Anticoagulant dosage was adjusted based on individual conditions to prevent clotting and bleeding.

Observation indicators

Sample collection

Before and after 6 months of treatment, 5 mL of fasting venous blood was collected in the morning. Blood was injected into a vacuum tube without an anticoagulant and left at 25 °C for 30 min. After clotting, blood was centrifuged at 3,000 rpm for 10 min. Serum was separated, aliquoted into sterile EP tubes, and stored at -80 °C for later testing to avoid repeated freezing and thawing.

Indicators detection

Inflammatory factors were detected using ELISA according to the manufacturer's instructions:

- hs-CRP (DKW12-2042-096, Shenzhen Dakewei Medical Device Co., Ltd., China)
- IL-6 (ml002859, Shanghai Meilian Biotechnology Co., Ltd., China)
- TNF-α (CSB-E04740h, Wuhan Huamei Bio-engineering Co., Ltd., China)

Serum samples were centrifuged (3,000 rpm, 10 min), aliquoted, and stored at -80 °C. Standards/samples (100 µL) were added to pre-coated antibody microplates (37 °C, 120 min). After washing five times, 100 µL HRP-labeled secondary antibody was added (37 °C, 60 min). TMB substrate (100 µL) was added for color development at 25 °C (in the dark, 15 min), followed by termination with 50 µL 2 mol/L H_2SO_4. Absorbance was read at 450 nm using a microplate reader (BioTek Synergy H1, USA).

Metabolic indicators

- BUN and Scr were determined using an AU5800 biochemical analyzer (Beckman Coulter, USA) and matching reagent kits via enzymatic methods.

- iPTH was determined using an electrochemiluminescence immunoassay (ECLIA) on a Roche Cobas e601 automatic analyzer with Elecsys PTH reagent kit (catalog no. 11731496).
- β2-MG was detected using a particle-enhanced turbidimetric immunoassay (PETIA) on a Siemens BN ProSpec automatic protein analyzer (Siemens, Germany) with N Latex β2-MG reagent kit (catalog no. OUGZ).

Novel biomarkers detection

- Oxidative stress markers: Malondialdehyde (MDA) and superoxide dismutase (SOD) were measured using colorimetric assay kits (Nanjing Jiancheng Bioengineering Institute, China). Absorbance was read at 532 nm (MDA) and 450 nm (SOD).
- Endothelial function marker: Endothelin-1 (ET-1) was quantified using a commercial ELISA kit (Cusabio, Wuhan, China, Cat# CSB-E07086h). The assay range was 1.56–100 pg/mL.
- Fibrosis marker: Transforming growth factor-beta1 (TGF-β1) was measured using an ELISA kit (R&D Systems, USA, Cat# DB100B). Serum samples were acid-activated before assay.
- Metabolic risk marker: Homocysteine (Hcy) was determined using an enzymatic assay on a Beckman AU5800 analyzer (Beckman Coulter, USA).

All samples were analyzed in duplicate. Inter- and intra-assay coefficients of variation were <10% for all novel biomarkers.

Statistical methods

Data were processed using SPSS 19.0 software. Measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and count data were expressed as rates (%). Differences were considered statistically significant at $P<0.05$. Paired t-tests were used for within-group comparisons, and independent t-tests for between-group comparisons.

Results

Statistics of primary diseases in subjects

In the AG, there were 12 cases of hypertensive nephropathy (34.29%), 11 cases of chronic glomerulonephritis (31.43%), 5 cases of chronic interstitial nephritis (14.29%), 19 cases of diabetic nephropathy (54.29%), 2 cases of obstructive nephropathy (5.71%), and 1 case of polycystic kidney disease (2.86%). In the BG, there were 15 cases of hypertensive nephropathy (40.54%), 15 cases of chronic glomerulonephritis (40.54%), 6 cases of chronic interstitial nephritis (16.22%), 19 cases of diabetic nephropathy (51.35%), 3 cases of obstructive nephropathy (8.11%), and 2 cases of polycystic kidney disease (5.41%). No significant difference was observed between groups ($P>0.05$).

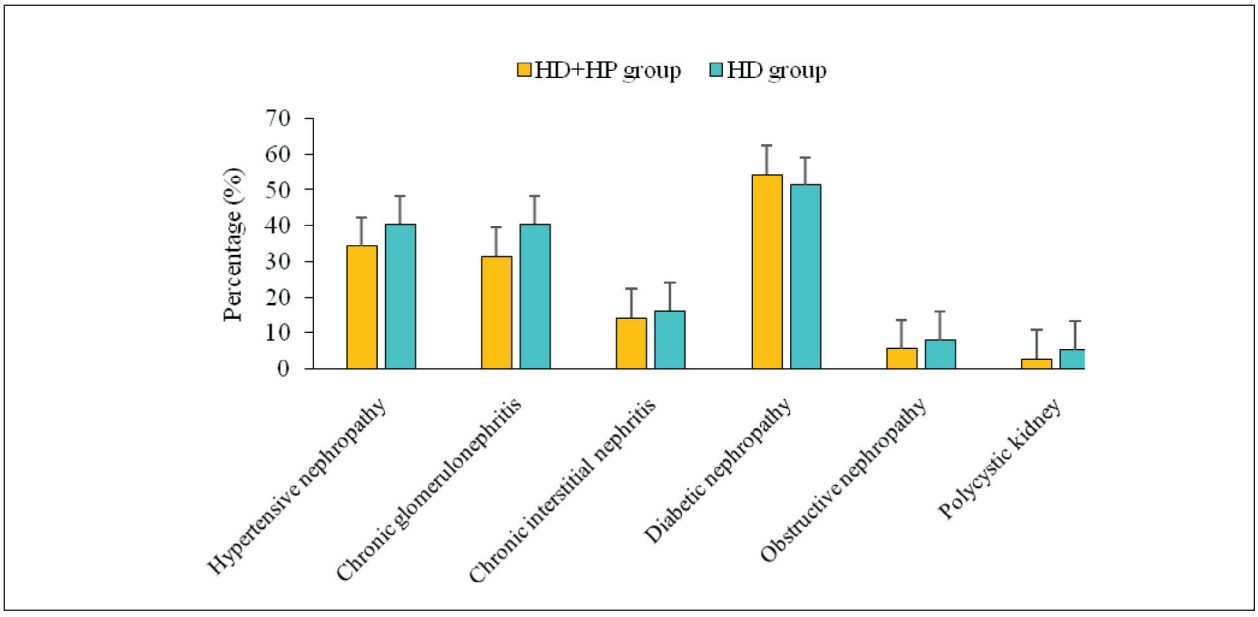

Figure 1 Statistics of primary diseases in subjects.

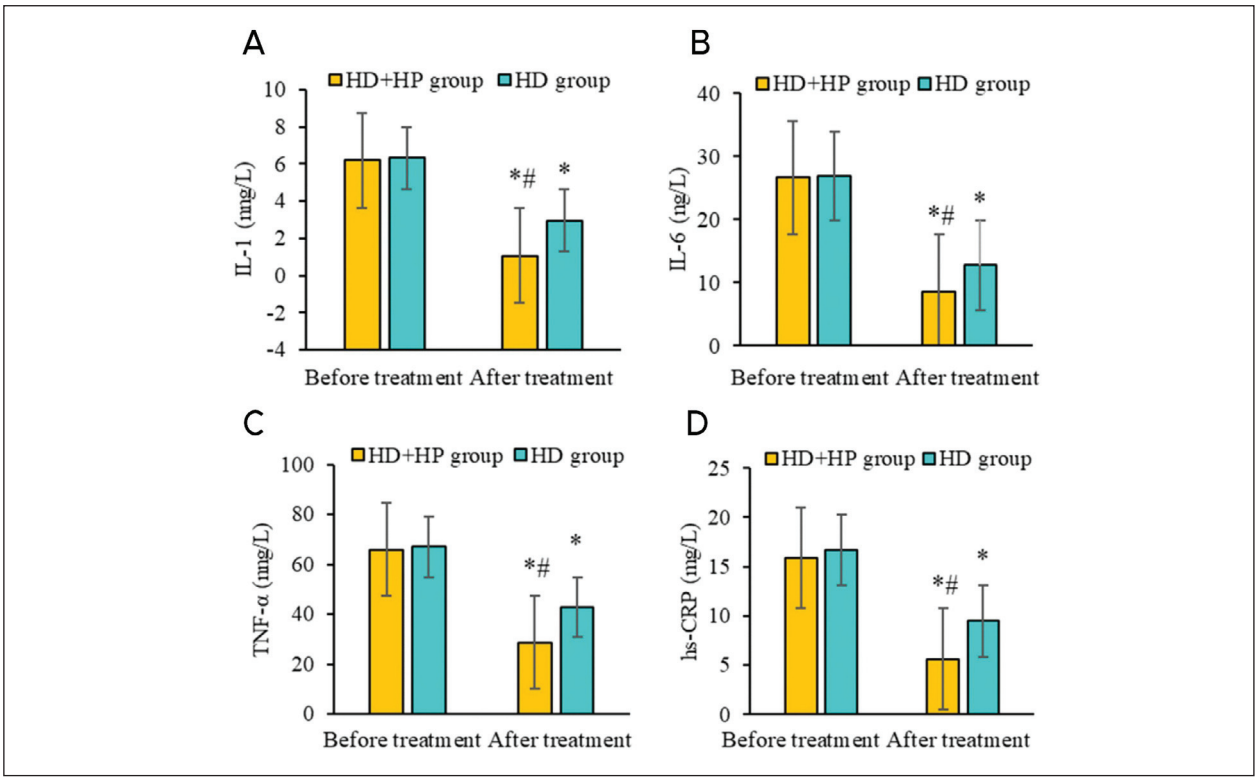

Figure 2 Contrast of inflammatory factors in subjects.

(Note: A: IL-1; B: IL-6; C: TNF-α; D: hs-CRP; # indicates visible distinction between AG and BG, * indicates visible distinction between post-remedy and pre-remedy, P<0.05)

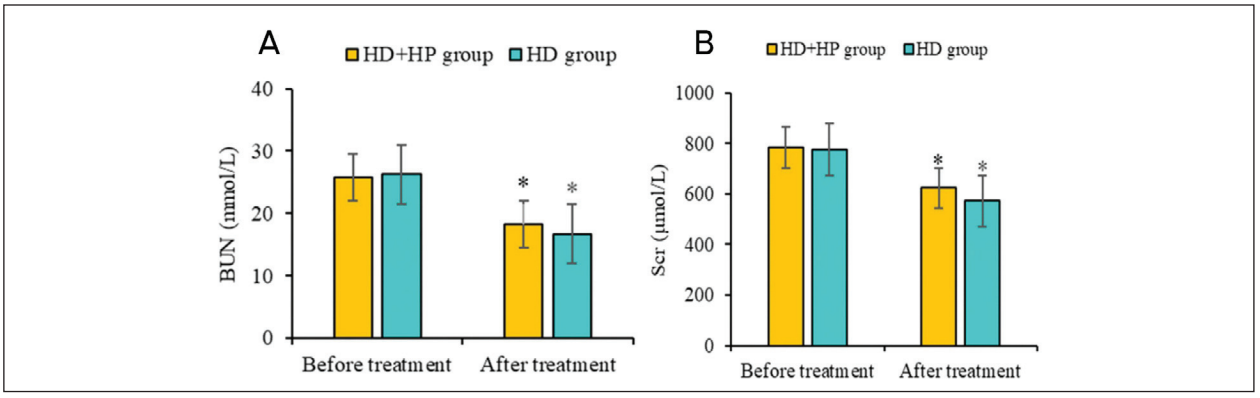

Figure 3 Contrast of BUN and Scr indicators in subjects.

(Note: A: BUN; B: Scr. * as against pre-remedy, P<0.05)

Comparison of inflammatory factors in subjects

All inflammatory factors (IL-6, TNF-α, and hs-CRP) were significantly reduced in the AG compared to the BG after treatment ($P<0.01$). For example, hs-CRP decreased from 15.87±2.41 mg/L to 5.61±3.21 mg/L in AG, versus 16.65±2.23 mg/L to 9.46±2.23 mg/L in BG.

Comparison of BUN and Scr in subjects

Both groups showed significant reductions in BUN and Scr after treatment ($P<0.05$), but there was no significant difference between groups post-treatment ($P>0.05$).

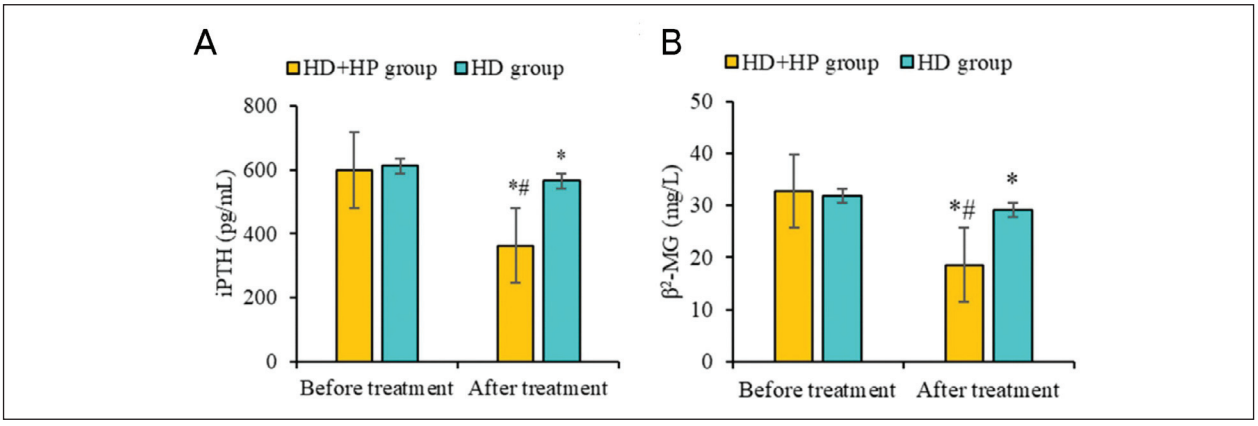

Figure 4 Contrast of iPTH and β2-MG indicators in subjects.

(Note: A: iPTH; B: β2-MG. * as against pre-remedy, # indicates visible distinction between AG and BG (P<0.05)

Table I Comparison of novel biomarkers before and after treatment ($\bar{x}\pm s$).

Biomarker	Group	Pre-treatment	Post-treatment	*P* (Within)	*P* (Between)
MDA (nmol/mL)	AG	8.42±1.56	4.21±0.98	<0.01	<0.01
	BG	8.39±1.61	6.88±1.32	<0.05	
SOD (U/mL)	AG	85.6±12.4	112.3±15.6	<0.01	<0.05
	BG	86.1±11.8	92.4±13.2	0.062	
ET-1 (pg/mL)	AG	7.45±1.89	3.12±0.76	<0.01	<0.01
	BG	7.52±1.92	5.89±1.21	<0.05	
TGF-β1 (ng/mL)	AG	45.6±8.9	22.3±5.4	<0.01	<0.01
	BG	46.1±9.2	38.7±7.1	<0.05	
Hcy (μmol/L)	AG	28.4±6.5	16.2±4.3	<0.01	<0.05
	BG	27.9±6.8	24.1±5.7	0.089	

Comparison of iPTH and β2-MG in subjects

iPTH and β2-MG levels were significantly lower in the AG compared to the BG after treatment (*P*<0.05). iPTH decreased by 42.3% in AG vs. a minimal change in BG.

Comparison of clinical efficacy

The total effective rate was 94.29% in AG vs. 81.08% in BG (*P*<0.05).

Comparison of novel biomarkers in subjects

Levels of oxidative stress, endothelial dysfunction, fibrosis, and metabolic risk markers are shown in *Table I*. Before treatment, no significant differences were observed between groups (*P*>0.05). After 6 months of treatment:

- Oxidative Stress: MDA levels decreased significantly in AG (from 8.42±1.56 nmol/mL to 4.21±0.98 nmol/mL) compared to BG (8.39±1.61 to 6.88±1.32 nmol/mL, *P*<0.01). SOD activity increased significantly in AG (from 85.6±12.4 U/mL to 112.3±15.6 U/mL) versus BG (86.1±11.8 to 92.4±13.2 U/mL, *P*<0.05).
- Endothelial Function: ET-1 levels were significantly lower in AG post-treatment (3.12±0.76 pg/mL vs. 5.89±1.21 pg/mL in BG, *P*<0.01).

Table II Contrast of adverse event incidence during remedy [n (%)].

Types of adverse events	AG (n=35)	BG (n=37)	RR (95%CI)	*P*
Hypotension	9 (25.0%)	11 (30.6%)	0.82 (0.39, 1.71)	0.601
Ultrafiltration paused	5 (13.9%)	6 (16.7%)	-	-
Saline expansion required	4 (11.1%)	5 (13.9%)	-	-
Coagulation events	6 (16.7%)	3 (8.3%)	2.00 (0.54, 7.44)	0.299
Perfusion device coagulation	4 (11.1%)	-	-	-
Dialyzer coagulation	2 (5.6%)	3 (8.3%)	-	-
Muscle spasm	7 (19.4%)	5 (13.9%)	1.40 (0.49, 3.98)	0.532
Allergic reactions	2 (5.6%)	1 (2.8%)	2.00 (0.19, 21.3)	>0.999
Perfusion device-related rash	2 (5.6%)	-	-	-
Dialyzer membrane-related pruritus	-	1 (2.8%)	-	-
Severe adverse events	1 (2.8%)	0 (0%)	-	>0.999
Blood loss >100 mL due to circuit disconnection	1 (2.8%)	-	-	-
Total incidence	22 (61.1%)	18 (50.0%)	1.22 (0.80, 1.87)	0.342

- Fibrosis Marker: TGF-β1 decreased significantly in AG (from 45.6±8.9 ng/mL to 22.3±5.4 ng/mL) compared to BG (46.1±9.2 to 38.7±7.1 ng/mL, $P<0.01$).
- Metabolic Risk Marker: Hcy levels were significantly reduced in AG (from 28.4±6.5 μmol/L to 16.2±4.3 μmol/L) versus BG (27.9±6.8 to 24.1±5.7 μmol/L, $P<0.05$).

Comparison of adverse events

No significant difference in total adverse event incidence was observed between groups (61.1% vs. 50.0%, $P=0.342$). Coagulation events were slightly higher in AG but were manageable with optimized anticoagulation.

Discussion

This study is the first to simultaneously evaluate the regulatory effects of HD+HP on the metabolic-inflammatory-oxidative-fibrotic network in CKD patients, confirming that combined therapy can selectively clear medium- and large-molecular-weight toxins, markedly improve the micro-inflammatory status, ameliorate oxidative stress and endothelial dysfunction, attenuate fibrotic pathways, and maintain a controlled safety profile (15–18).

Due to reduced kidney function, CKD patients experience accumulation of toxins, especially medium/large molecular toxins and inflammatory factors, which can cause various complications and severely affect quality of life (19). Traditional HD effectively removes small molecular toxins such as urea and creatinine but has limited ability to clear medium- and large-molecular toxins. HP, using adsorbents, can effectively remove these toxins, compensating for HD's shortcomings (20, 21). The results suggested that after 6 months of remedy, iPTH and β2-MG levels in the AG were markedly lower than those in the BG, with a 42.3% reduction in iPTH. Long-term accumulation of iPTH can lead to serious complications like renal osteodystrophy and vascular calcification, while β2-MG accumulation is closely associated with dialysis-related amyloidosis. HP effectively removed these medium- and large-molecular-weight toxins through adsorption, improving calcium-phosphorus metabolism and reducing the risk of related complications.

An elevated systemic inflammatory response index independently increases the risk of all-cause and cardiovascular mortality in CKD patients (22). This article found that, following the remedy, the median hs-CRP decreased from 12.6 mg/L to 5.2 mg/L in the AG. HP not only removes inflammatory factors but may also inhibit their production by reducing toxin-induced immune system stimulation,

thereby alleviating systemic inflammatory responses. This is crucial for improving patients' cardiovascular prognosis and overall quality of life.

In addition to traditional metabolic and inflammatory markers, this study incorporated novel biomarkers reflecting oxidative stress, endothelial dysfunction, fibrosis, and metabolic risk. The significant reduction in MDA and increase in SOD activity in the HD+HP group suggest that combined therapy ameliorates oxidative stress – a key driver of CKD progression and cardiovascular complications (23). The decrease in ET-1 indicates improved endothelial function, which may contribute to reduced cardiovascular risk (24). Lower TGF-β1 levels suggest attenuation of fibrotic pathways, potentially slowing renal tissue remodeling (25). The reduction in Hcy highlights the role of HP in clearing protein-bound and medium-molecular-weight toxins that contribute to hyperhomocysteinemia, a known cardiovascular risk factor in CKD patients (26).

These findings expand the understanding of HD+HP's multimodal benefits beyond toxin removal to include modulation of oxidative, endothelial, fibrotic, and metabolic pathways. This comprehensive biomarker profile supports the use of HD+HP as a holistic blood purification strategy, particularly for patients with high oxidative stress, endothelial dysfunction, or progressive fibrosis (27).

Regarding small-molecular-toxin removal, both groups reported post-remedy reductions in BUN and Scr, with no differences among subjects. This indicates that HD+HP therapy, without affecting small-molecular-toxin removal, effectively clears medium- and large-molecular toxins and inflammatory factors through HP's synergistic effect, achieving a more comprehensive blood-purification effect.

There was no statistically significant difference in the incidence of adverse events among the subjects. Although the incidence of coagulation events was slightly higher in the AG, it could be effectively controlled by optimizing the anticoagulation protocol, and no serious adverse events occurred (28–30).

The results of this article are consistent with previous studies on HD+HP therapy (11), further confirming its advantages in clearing medium- and large-molecular-weight toxins and improving the inflammatory status. With a longer observation period (6 months) and simultaneous monitoring of metabolic indicators, inflammatory factors, and novel biomarkers, this article provides a systematic assessment of the metabolic-inflammatory-oxidative network linkage. It offers stronger, evidence-based support for the clinical application of HD+HP therapy.

Conclusion

This article confirms that HD+HP is markedly superior to HD alone in improving clinical outcomes, clearing medium- and large-molecular-weight toxins, inhibiting microinflammation, and ameliorating oxidative stress, endothelial dysfunction, and fibrosis in CKD patients. Combined therapy can more effectively remove pro-inflammatory factors, reduce oxidative damage, improve endothelial function, attenuate fibrotic pathways, and alleviate systemic micro-inflammatory responses. HD+HP can specifically reduce the accumulation of toxins associated with the risk of renal osteodystrophy and dialysis-related amyloidosis. Combined therapy can substantially improve patients' clinical symptoms and quality of life. By synergistically removing large molecular toxins and inflammatory mediators, HD+HP provides an effective multisystem strategy for delaying CKD complications, especially suitable for patients with refractory high iPTH/β2-MG, micro-inflammatory status, or elevated oxidative/fibrotic biomarkers.

Acknowledgments. The authors thank all participants and medical staff involved in this study.

Authors' contribution

All authors contributed to the study conception and design. Nijun Zheng and Xuepeng Yan performed material preparation, data collection, and analysis. The first draft of the manuscript was written by Haitao Lu, Tonghe Song, and Jixiang Zhao; Ming Cai commented on earlier versions. All authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Data availability statement

All data generated or analyzed during this study are included in this published article.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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Recieved: December 25, 2025
Accepted: February 02, 2026