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ORIGINAL ARTICLE

Effectiveness of haemodialysis with hemoperfusion therapeutic modality in paediatric chronic kidney disease

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ABSTRACT

Introduction Children undergoing routine kidney replacement therapy often experience hyperinflammation state that manifests as anorexia and increasing levels of β-2 microglobulin (B2M) in the blood.
Aim To assess the reduction of inflammation by examining ferritin and B2M serum levels in children with end-stage kidney disease (ESKD) who were receiving a combination of haemodialysis and hemoperfusion (HDHP).
Methods This retrospective cohort study research utilized data from medical records, focusing on children with chronic kidney disease (CKD) who received haemodialysis between January 2020 and December 2022. If a patient exhibits reduced food intake and appetite, a B2M serum test is warranted. An elevated B2M level in patients indicates the need for haemodialysis-hemoperfusion (HDHP). Prior to each procedure, including HDHP and blood sampling, an informed consent was obtained both from patients and their legal guardians.
Results HDHP significantly reduced urea, ferritin, and B2M levels in children with ESKD ($p<0.001$). There was a weak positive correlation between ferritin and B2M levels, with $r=0.195$ (95% CI: 0.003–1.000; $p=0.043$).
Conclusion This result implies that higher ferritin levels are linked to a notable increase in B2M levels.
Keywords: children, cardiovascular, chronic kidney disease, haemodialysis, hemoperfusion

INTRODUCTION

End-stage kidney disease (ESKD) is increasingly recognized as an inflammatory condition, with middle molecules like ß-2 microglobulin (B2M) playing a crucial role in triggering various cardiovascular issues. Consequently, there is a strong justification for expanding research into synergistic strategies that integrate hemoperfusion (HP) with other dialysis methods to achieve complementary metabolite removal, prevent complications, and enhance patient outcomes (1). Patients with ESKD are susceptible to complications such as malnutrition, muscle wasting, and heart-related issues. Several studies have indicated that these problems are linked to an increase in medium-weight uremic toxins, including beta-2 microglobulin (2,3) SETTING, PARTICIPANTS, & MEASUREMENTS: The Filtration in the Neuropathy of End-Stage Kidney Disease Symptom Evolution (FINESSE.

Arterial stiffness is linked to the progression of ESKD through a series of mechanisms involving oxidative stress and proinflammatory cytokines (4,5)the most common histopathological form of SRNS. This study demonstrated a correlation between the levels of blood TGFB and its related microRNAs (miRNAs). Chronic kidney disease (CKD) leads to alterations in vascular structure and function, which have significant hemodynamic consequences (4) the most common histopathological form of SRNS. This study demonstrated a correlation between the levels of blood TGFB and its related miRNAs. In CKD patients, early arterial stiffening results from the interplay between oxidative stress and persistent vascular inflammation, causing rapid decline in left ventricular function and changes in tissue perfusion (4)the most common histopathological form of SRNS. This study demonstrated a correlation between the levels of blood TGFB and its related miRNAs. CKD enhances the inflammatory cascade's activation, disrupting endothelial function, increasing vascular tone, thickening vessel walls, and promoting calcium deposits in the arterial walls (4)the most common histopathological form of SRNS. This study demonstrated a correlation between the levels of blood TGFB and its related miRNAs. Concurrently, autonomic imbalance and changes in other hormonal systems also contribute to overactivation of inflammatory and fibrotic mediators (6). Consequently, hormonal imbalances also play a role in causing structural and functional damage throughout the arterial wall (6). The connection between serum ferritin levels and arterial stiffness may be linked to oxidative stress (7). Ferritin transcription is mainly active during inflammatory states, while it can only be triggered by exposure to extremely high levels of iron. Pro-inflammatory cytokines influence the

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balance between ferritin and body iron storage by enhancing ferritin production (8) causing increased mortality. Ferritin stores iron, representing iron status. Hepcidin binds to ferroportin, thereby inhibiting iron absorption/efflux. Inflammation in CKD increases ferritin and hepcidin independent of iron status, which reduce iron availability. While intravenous iron therapy (IIT). Ferritin, with a molecular weight of 19000 Daltons, contributes to vascular stiffness associated with CKD, similar to B2M, which weighs 11800 Daltons. Additionally, other pro-inflammatory molecules like TNF-alpha also have a molecular weight of approximately 19000 Daltons (9).

Hemoperfusion (HP) involves passing blood through a column filled with resin granules that serve as adsorbents (10). This procedure relies on a concentration gradient between the blood and the solvent across the dialysis membrane (11). HP is used to eliminate liposoluble substances that are bound to plasma proteins and have a lower molecular weight, especially when the blood flow through the device is higher (12–15).

HP serves as an effective adjunct in haemodialysis for both acute kidney injury (AKI) and advanced stages of CKD, where the targeted elimination of harmful proteins is necessary (16,17). Eliminating harmful pathogens can be crucial for survival in situations of excessive inflammation. HP possesses a distinctive capability to adsorb molecules with a high molecular weight and exhibits a strong affinity for binding proteins. (10,18,19) The European Uremic Toxin Group categorizes uremic toxins into three distinct types: (1) small water-soluble toxins with a molecular weight (MW) of less than 500 Da, such as urea and creatinine; (2) middle molecules with an MW of 500 Da or more, including parathyroid hormone (PTH), C-reactive protein, and β2-microglobulin (B2M), which can be effectively eliminated through hemofiltration (HF) and high-flux haemodialysis (HD); and (3) protein-bound solutes, like homocysteine, which are not removed by traditional HD or HF (16,20). Conventional haemodialysis methods that rely on diffusion and convection face certain limitations due to the permeability characteristics of the membrane (18). The high mortality rate linked to cardiovascular diseases and the outcomes for ESKD patients undergoing HD, have been associated with blood levels of medium to large molecules that are not adequately removed by KRT (21). The HA 130 cartridge contains an electrically porous resin with molecular weights ranging from 10 to 60 kDa, designed to selectively eliminate cytokines, complements, and other endotoxins. Research on HA 130-based hemoperfusion (HP) has been conducted across various groups, particularly in the context of inflammatory conditions such as cytokine storms (16,19).

Chu et al. found that using the same cartridge in conjunction with pulse high-volume HF in patients with septic shock resulted in positive effects on cardiovascular physiology and more significant reductions in IL-6, IL-10, and TNF-α levels compared to those who underwent continuous venous-venous HF (16,22) advances in adsorption materials (e.g., new synthetic polymers, biomimetic coating, and matrixes with novel structures). From a prognostic standpoint, a systematic review and meta-analysis indicated that combining HD with HP enhances survival rates. The notable decrease in myocardial enzyme levels linked to the joint use of HP and HD strongly implies that their simultaneous application might lower cardiovascular issues and safeguard the myocardium. Similarly, in research conducted by Raine et al., besides a more significant reduction in inflammatory biomarkers, there was a notable improvement in nutritional status indicators in the group receiving both HD and HP (16,23–25) highly protein bound or large molecular weight uremic toxins such as phenolic and indolic compounds and homocysteine, which are associated with adverse outcomes such as cardiovascular disease of patients with ESRD, are difficult to remove via HD but can be effectively eliminates by haemoperfusion (HP).

For patients with ESKD who are already regularly receiving HD, it is recommended to routinely incorporate HDHP sessions, ideally alternating with HD, to mitigate the effects of diminished residual kidney function (26). Numerous other studies indicate that HDHP is implemented due to elevated B2M levels, reduced appetite, itching, and various hyperinflammatory conditions (10, 24–27) pruritus.

Given the scarcity of B2M testing in developing nations, it is essential to investigate alternative biomarkers that align with B2M in hyperinflammatory conditions. Ferritin, a protein that often sees increased expression during such states, is being studied by researchers to understand its connection with B2M expression in children suffering from ESKD (28–32). While numerous children with CKD seem to be experiencing a hyperinflammatory condition, there is still a lack of extensive research on HDHP in the paediatric population.

The aim of this study was to assess the reduction of inflammation by examining ferritin and B2M serum levels in children with end-stage kidney disease (ESKD) undergoing combined haemodialysis and hemoperfusion (HDHP) therapy.

PATIENTS AND METHODS

Patients and study design

A cross-sectional study was carried out using medical records of children with ESKD who regularly underwent HD at the haemodialysis unit of Hasan Sadikin General Hospital between January 2020 and December 2022. During the monitoring of children with CKD, those who showed signs of anorexia were regularly tested for ferritin and B2M level. The study included children with NS, aged 0 to 18 years, who had ESKD and either elevated B2M or ferritin levels, or a reduced appetite. Children with cancer or blood disorders who received regular blood transfusions were not included. Additionally, those with decreased appetite due to acute respiratory infections, gastrointestinal diseases, or uremic gastropathy were excluded.

These children typically have physical and laboratory tests during each haemodialysis session, which occurs 2 to 3 times weekly. For children with reduced appetite, ferritin and B2M levels were checked, and if elevated B2M level was detected, HDHP (Jafron HA130) was administered. In cases where children did not receive HDHP, their serum ferritin and B2M levels were reassessed following HDHP and were regularly followed up every month.

A consent for participation was obtained from patients' legal guardians, following the guidelines of the Declaration of Helsinki.

The ethics committee of Universitas Padjadjaran granted an approval for this research under No. 1030/UN.KEP/EC/2021.

Methods

The duration of HDHP ranges from 4 to 6 hours, with a blood flow rate of 3 to 5 mL/per kg of body weight. The dialysate flow was set at twice the volume of the blood flow, and the ultrafiltration target was tailored to each patient's intravascular condition, assessed through physical examination and addi-

tional tests like point-of-care ultrasound, which evaluates the inferior vena cava to aortic ratio (33,34). The hemoperfusion technique utilizes a Jafron HA130 cartridge in conjunction with a B-Braun dialysis machine.

Statistical analysis

A correlation analysis was conducted among ferritin, B2M, and urea. The Wilcoxon test was used to examine the variations in urea, B2M, and ferritin levels before and after HDHP. Spearman's rho was employed to assess the correlation between B2M and ferritin levels.

RESULTS

Out of 95 children who underwent routine HD, we excluded 16 participants: one child was over 18 years of age during follow-up, and 15 children could not have their B2M level measured. The average age was 13.7 years, suggesting that the majority of ESKD patients were teenagers. The gender distribution was fairly balanced, with females and males comprising 48.1% and 59.1%, respectively. Therefore, the study population was relatively homogeneous, primarily consisting of adolescents with a similar gender distribution (Table 1). In this study, the number of children with ESKD who were candidates for HDHP was similar for both genders; all patients receiving HDHP had an underlying glomerular condition, specifically steroid-resistant nephrotic syndrome (SRNS).

Table 1. Characteristics of 79 end-stage kidney disease patients

Variables	Results
Age (Mean±SD)	13.7±2.3
Gender (No; %)	
Male	38 (48.1)
Female	41 (51.9)
eGFR (mL/min/1.73m2) (Mean±SD)	5.1 (1.2)
Potassium (mg/dL) (Mean±SD)	4.3 (1.2)

eGFR, estimated glomerular filtration rate

The average ferritin level prior to HDHP was 1352±636 ng/mL ng/mL. The median ferritin level stood at 1030 ng/mL with an interquartile range (IQR) 850–2034 ng/mL. The mean ferritin level following HDHP dropped to 764±462 ng/mL ng/mL. The median ferritin level decreased to 670 ng/mL (IQR of 449–1107 ng/mL). The reduction in ferritin levels was statistically significant ($p < 0.001$) (Table 2).

Table 2. Changes in ferritin, urea and B2M levels before and after haemodialysis hemoperfusion (HDHP) in paediatric patients with end-stage kidney disease patients (ESKD)

Variables	Before HDHP	After HDHP	p*
Ferritin			
Mean ± SD	1352±636	764±462	<0.001
Median (IQR)	1030 (850 – 2034)	670 (449 – 1107)	
Urea			
Mean ± SD	229±36	113±23	<0.00
Median (IQR)	231 (212 – 245)	109 (101 – 121)	
B2M			
Mean ± SD	34±9	14±6	<0.001*
Median (IQR)	33 (27 – 39)	13 (9 – 18)	

*Wilcoxon test; p<0.05

Prior to HDHP, the average urea level was 229±462 ng/mL, with a standard deviation of 36 mg/dL. The median urea level stood at 231 mg/dL (IQR: 212–245 mg/dL). Following HDHP, the mean urea level dropped to 113±23 mg/dL. The median urea level fell to 109 mg/dL (IQR: 101–121 mg/dL) ($p < 0.001$). Regarding B2M, before HDHP, the mean level was 34±23 ng/mL. The median B2M level was 33 ng/mL, (IQR: 27–39 ng/mL). After HDHP, the mean B2M level decreased to 14±6 ng/mL. The median B2M level dropped to 13 ng/mL (IQR: 9–18 ng/mL) ($p<0.001$). Overall, these findings suggest that HDHP effectively lowers ferritin, urea, and B2M levels in paediatric patients with ESKD, demonstrating the procedure's efficacy in reducing these substances in the blood (Figure 1).

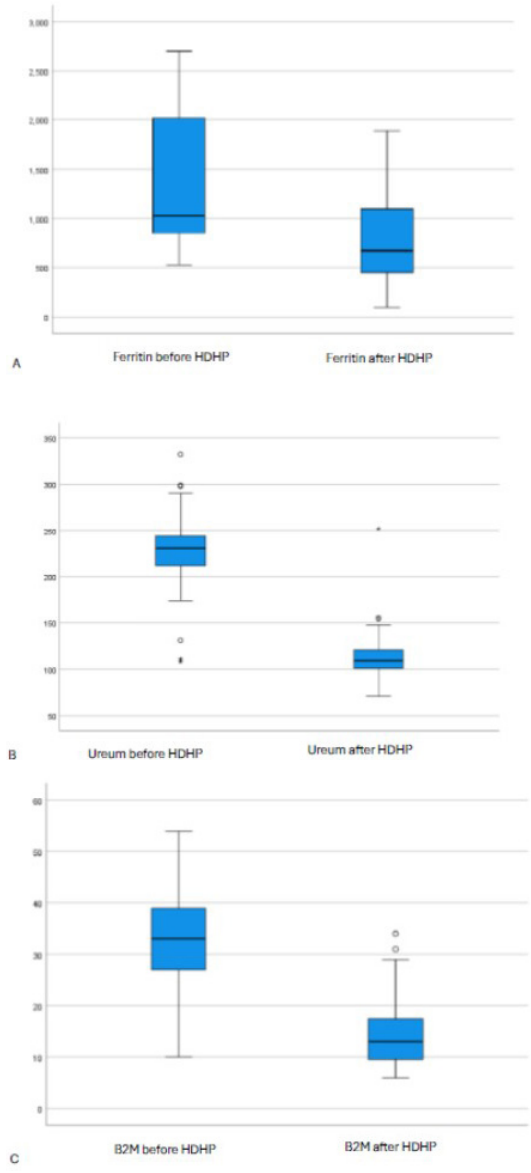

Figure 1. Changes before and after hemoperfusion haemodialysis (HDHP) in paediatric patients with end-stage kidney disease patients (ESKD). A) in ferritin level; B) in urea level; C) in B2M level.

There was a very weak inverse correlation between ferritin and B2M levels before HDHP, $r= -0.050$ (95% CI: -1.000 to 0.038; $p=0.332$) (Table 3). This indicates that higher ferritin levels were slightly linked to lower B2M levels. However, this association was not statistically significant (Figure 2A).

Urea and B2M: There was a relatively strong positive correlation between urea level and B2M before HDHP, $r=0.364$ (95% CI: 0.185 to 1.000; $p<0.001$). This suggests that an increase in

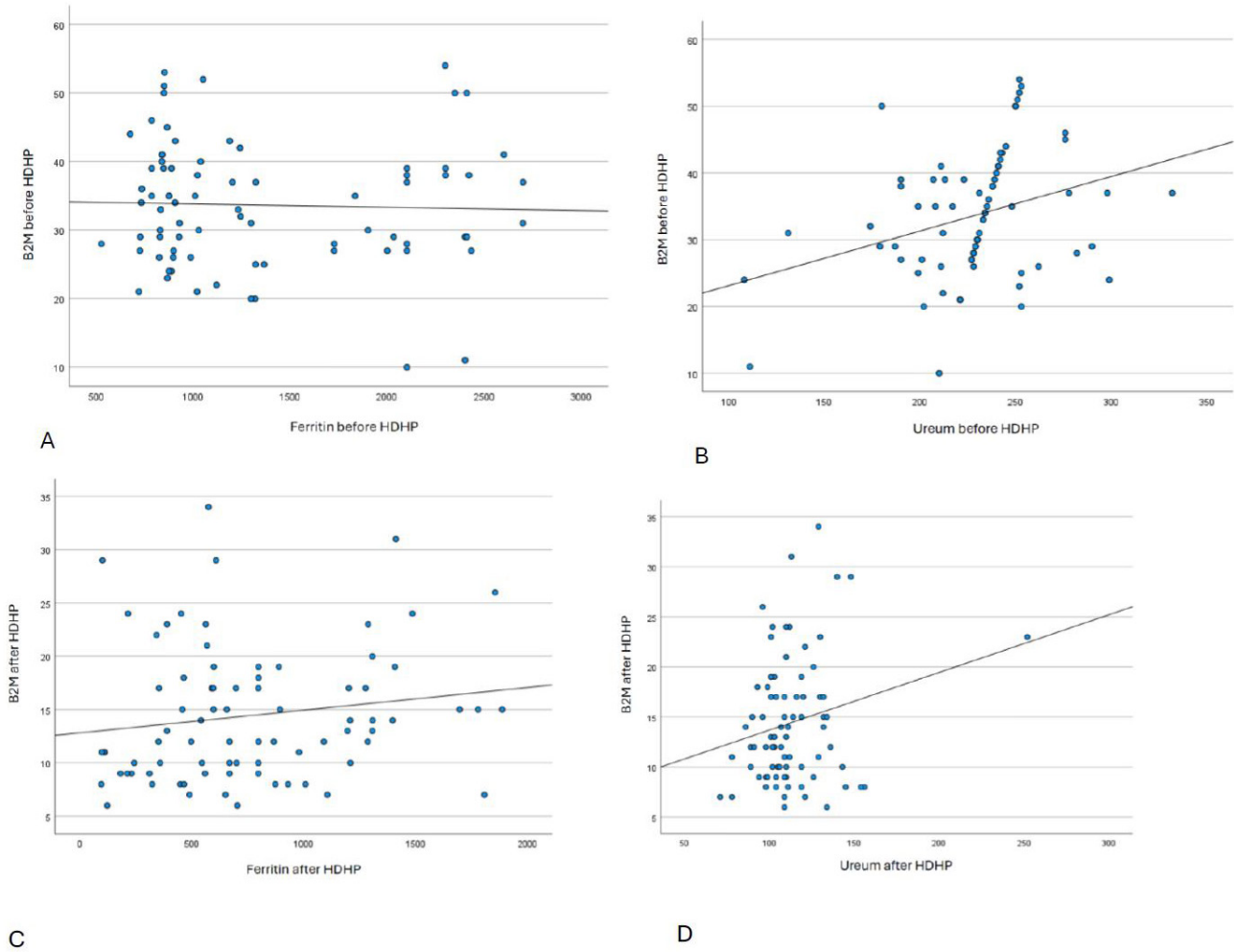

Figure 2. Scatterplot of: A) ferritin level against B2M before hemoperfusion haemodialysis (HDHP); B) urea level against B2M before HDH; C), ferritin level against B2M after HDHP; D) urea level against B2M after HDHP in paediatric patients with end-stage kidney disease patients (ESKD)

urea level was significantly associated with an increase in B2M level (Figure 2B).

There was a weak positive correlation between ferritin and B2M levels after HDHP, r=0.195 (95% CI: 0.003-1.000; p=0.043. This implies that higher ferritin level was significantly associated with increased B2M level, although the correlation is weak (Figure 2C).

A very weak positive correlation between urea level and B2M after HDHP was found, r=0.113 (95% CI: -0.080 to 1.000; p=0.160). This indicates that higher urea level was slightly linked to higher B2M level; however, this association was not statistically significant (Figure 2D). Overall, a significant positive correlation between urea and B2M level before HDHP was found, while no significant correlation was found between ferritin and B2M level. After HDHP, a significant correlation emerged between ferritin and B2M level, but the correlation between urea and B2M levels was no longer significant. The shift in correlation direction suggests that HDHP affects the relationship between these variables in paediatric patients with ESKD (Table 3).

Table 3. Correlation of ferritin, urea and B2M levels before and after haemodialysis hemoperfusion (HDHP) in paediatric patients with end-stage kidney disease patients (ESKD)

Variable		B2M	
		r (95% CI)	p
Before HDHP	Ferritin	-0.050 (-1.000 – 0.038)	0.332
	Ureum	0.364 (0.185 – 1.000)	<0.001
After HDHP	Ferritin	0.195 (0.003 – 1.000)	0.043
	Ureum	0.113 (-0.080 – 1.000)	0.160

r, correlation coefficient (using Spearman's rho correlation); p<0.05

DISCUSSION

The children in the present study had not undergone a kidney biopsy because their families did not consent; thus, we conducted the biopsy during kidney transplantation. In ESKD patients with glomerular disease, a humoral response can lead to progressive fibrosis in various organs. This fibrosis results from overproduction of proinflammatory mediators, primarily miR-433, transforming growth factor β (TGF-β) and vascular endothelial growth factor (VEGF) (4,35–38). In hospital service settings within developing nations, the examination of these two mediators is not yet readily accessible. However, B2M testing has begun to be implemented in these countries, with numerous studies validating its effectiveness in identifying the need for HDHP or hemodiafiltration (HDF) (24).

Notable variations were detected in the concentrations of urea, B2M, and ferritin before and after HDHP. HDHP, which combines HD with hemofiltration, requires precise measurement. In this study, HD in children demonstrated good adequacy, as evidenced by decreased blood urea levels, with all cases show-

ing a urea reduction rate (URR) exceeding 65%. Our aim was to achieve the clearance of large molecular weight (MW) molecules and those with high protein-binding affinity, as indicated by the analysis of B2M and ferritin, which represents these medium-sized molecules (39,40)the aforementioned agents are nearly impossible to be given. Also, the COVID-19 disease has a huge impact in all countries in the world, including in nephrology and other immunocompromized patients in children. The problems caused by this disease are also exacerbated by the economic conditions of poor and developing countries. It is challenging for clinicians in poor and developing countries to take advantage of alternative modalities for the management of the disease. Therapeutic plasma exchange (TPE). In these children, there was a notable reduction in B2M and ferritin levels. This indicates that other cytokines of similar size to B2M and ferritin are also effectively removed, which is beneficial for slowing the progression of ESKD associated with glomerular disease, as it manifests through a decline in remaining kidney function. The study also observed a correlation between the reduction in B2M level and ferritin level following HDHP, suggesting that ferritin can serve as a proxy for B2M in monitoring HDHP in children with ESKD in resource-limited settings. A limitation of this research is that HDHP could only be conducted once due to financial constraints. Most hospital does not receive national health insurance funding for HDHP cartridges and B2M tests, so we rely on external support. Further studies are necessary over an extended period, particularly to assess survival outcome in paediatric ESKD patients undergoing HDHP, with a focus on survival linked to reduced cardiovascular function.

Research on HDHPs in children has not been well published; therefore, studies on adult populations are a prototype (16,22) advances in adsorption materials (e.g., new synthetic polymers, biomimetic coating, and matrixes with novel structures). A systematic review and meta-analysis revealed that combining HD and HP enhanced survival rates. The significant decrease in myocardial enzyme level linked to the joint use of HP and HD strongly indicates that their simultaneous application might lower cardiovascular issues and safeguard the myocardium. Raine et al. noted that, in addition to a more substantial reduction in inflammatory biomarkers, there was a notable improvement in nutritional status indices in the group receiving both HD and HP (16,23–25)highly protein bound or large molecular weight uremic toxins such as phenolic and indolic compounds and homocysteine, which are associated with adverse outcomes such as cardiovascular disease of patients with ESKD, are difficult to remove via HD but can be effectively eliminates by HP.

For patients with ESKD who are already regularly receiving HD, it is recommended to routinely incorporate HDHP sessions, ideally alternating with HD, to mitigate the effects of diminished residual kidney function (26). Numerous other studies indicate that HDHP is implemented due to elevated B2M levels, reduced appetite, itching, and various hyperinflammatory conditions (24) pruritus.

Research has shown that HDHP effectively reduces cardiovascular incidents in patients with uraemia by managing hypertension (41). Endothelial cell dysfunction, imbalances in the renin-angiotensin system, hyperparathyroidism, heightened sympathetic nerve activity, excessive erythropoietin usage, significant fluid overload, and sodium retention are all linked to the pathogenesis (29). Haemodialysis primarily operates on the concept of a semipermeable membrane and the diffusion of solutes. Solutes migrate towards the area of lower concentration, influenced by the concentration gradient between the solutions on either side of the membrane. On one side, all metabolic waste products are expelled from the body to maintain internal stability, while on the other side, excess fluids are removed to enhance the management of water and sodium levels (30). Nonetheless, some patients undergoing haemodialysis continue to experience high blood pressure even after their treatment sessions. The current strategies for managing uraemia in these patients show limited effectiveness (31). Hemofiltration (HF) is a technique for purifying blood that efficiently eliminates medium- and large-sized molecules. This approach employs a dialysis membrane with high permeability to filter out various toxins from the bloodstream and enhances the ultrafiltration rate when combined with haemodialysis. According to Xu et al., HDHP is effective in managing uraemia complicated by resistant hypertension. Another study indicated that the combination of haemodialysis with hemofiltration or hemoperfusion is a successful method for treating uraemia with refractory hypertension. This technique effectively regulates blood pressure in patients and enhances cardiac function.

Furthermore, it aids in the removal of toxic metabolites, lowers the risk of adverse reactions, and is safe for clinical use (41). The method is highly effective in enhancing clinical symptoms and sustaining the physiological parameters of patients.

In conclusion, HDHP is an effective approach for managing hyperinflammatory conditions in children with ESKD. Moreover, in situations where the B2M modality is unavailable, ferritin can be utilized to guide the management of HDHP in children.

AUTHOR'S CONTRIBUTION

AW, writing manuscript, collecting subjects, editing; RR, manuscript editing; DR, manuscript editing and supervising; DH, supervision and fund managing

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