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Study of Effect of High-Flux Versus Low-Flux Dialysis Membranes on Parathyroid Hormone

Ahmed Rabie El Arbagy[1], Mahmoud Abd El Aziz Koura[1], Abd El Samad Sobhy Abou El Nasr[2], Hany Said Elbarbary[1,*]

[1]Departments of Internal Medicine, Faculty of Medicine, Menoufia University, Menoufia, Egypt
[2]Internal Medicine Department, Benha teaching hospital, Qalyobia, Egypt
*Corresponding author: hanyelbarbary2004@yahoo.com

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Abstract **Objective:** Investigate the influence of permeability of low-flux versus high-flux dialysis membranes on intact PTH during hemodialysis. **Background:** Hyperparathyroidism is a common finding in patients with renal insufficiency and parathyroid hormone (PTH) is considered a uremic toxin responsible for many of the abnormalities of the uremic state and bone disease. **Materials and Methods:** Forty adult patients on regular hemodialysis were enrolled in a prospective study. Low-flux polysulfone membranes were used for at least 6 months and then the patients were switched to use high-flux polysulfone membranes for 1 month. Serum electrolytes and intact PTH before and after dialysis were compared before and after changes in dialysis membrane. **Results:** At the end of the 1-month use of high-flux filters, predialysis intact PTH level (415.96 ± 226.72 ng/dL) showed a significant decline ($P < 0.05$) compared to the predialysis intact PTH (312.28 ± 191.98 ng/dL) with low-flux membranes. Intact PTH level correlated negatively with serum calcium and positively with serum phosphorus levels only in the predialysis samples with the use of low-flux but not high-flux filters. **Conclusion:** High-flux dialysis membranes are more efficient in removal of intact PTH, one of the middle-sized uremic toxins, than low-flux membranes.

Keywords: *Parathyroid hormone, ESRD, hemodialysis membrane*

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1. Introduction

While a number of therapies and technologies have been reported to increase health-related quality of life in patients with chronic kidney failure, patients report that they remain substantially burdened by limited physical functioning and by dialysis-related symptoms [1].

Health-related quality of life has been associated with nutritional outcomes, hospitalizations, and survival in patients with End-stage renal disease (ESRD).Quality of life in ESRD patients on dialysis is also dependent on the quality of dialysis [2].

Three general types of dialysis membranes are available at present: unmodified cellulose (low flux; namely "bioincompatible" membranes), modified/regenerated cellulose (low flux or high flux; namely, "relatively biocompatible"), and synthetic (low flux or high flux; namely "relatively biocompatible") [3].

The choice of a dialysis membrane should take into account the following: biocompatibility of the material towards leucocytes and complement activation; blood volume priming requirement, which is membrane area related; and permeability, determined in the simplest way by two characteristics of hydraulic permeability and molecular permeability determined at least by molecular weight of the molecule considered [4].

Uremic toxins are classified into 3 groups: small (< 500 Da) water soluble molecules such as urea, sodium, and phosphate, which are rapidly produced in intracellular compartment and are efficiently removed by most filters; middle-sized (500 to 40 000 Da) water soluble molecules such as β2-microglobulin, parathyroid hormone (PTH), some cytokines (interleukin-6 and tumor necrotizing factor) that require optimized filter design and convection for removal; and small (< 500 Da) but protein bound molecules which are poorly removed with traditional dialysis [5].

In fact low-flux membranes do not remove middle-sized molecule toxin but highly permeable membranes are efficient in removal of both small non-protein bound and middle-sized uremic toxins [4].

Hyperparathyroidism is a common finding in patients with renal insufficiency. Calcitriol deficiency and phosphate retention together with hypocalcemia are the main factors involved in the pathogenesis of secondary hyperparathyroidism **[6]**.

During hemodialysis, there is a decrease in serum PTH levels caused by the influx of calcium from the dialysate to blood. At the same time, during the first one to two hours of hemodialysis, there is a decrease in serum

phosphate that potentially could directly affect PTH secretion [7].

Parathyroid hormone in haemodialysis patients is affected by ionized calcium and dialysis membrane and also by the use of calcium-containing phosphate binders and vitamin D analogues which both have been shown to suppress PTH release and improve the related bone disease [8]. The aim of our study was to investigate the influence of permeability of low-flux versus high-flux dialysis membranes on intact PTH during hemodialysis.

2. Patients and Methods

This study was conducted on 40 adult patients who present with end stage renal disease and under regular hemodialysis in Hemodialysis Unit, Benha Teaching Hospital, Qalyobia, Egypt during the period from January 2013 to August 2013. They were 20 males and 20 females. All patients with minimum dialysis duration of 6 months were included. Patients who had parathyroidectomy with or without replacement therapy were excluded.

All patients were on conventional hemodialysis, 4-hour session, 3 times per week using hemodialysis machine (Fresenius Medical Care 4008B) with low flux polysulfone filters (Fresinius F6). The standard dialysis bath consisted of sodium, 103 mEq/L; potassium, 2 mEq/L; calcium, 1.75 mEq/L; and bicarbonate, 35 mEq/L. All patients were switched to high flux polysulfone filters (F6) for one month duration without changing any of the other dialysis prescription parameters (except for ultrafiltration to reach their optimal dry weight). Dry body weight was defined as the postdialysis body weight below which the patients developed symptomatic hypotension or muscle cramps in the absence of edema).

Patients were clinically evaluated; serum electrolytes and intact PTH before and after dialysis were compared before and after changing the dialysis membrane. Moreover, the doses of vitamin D analogues or phosphate binders were kept constant through the study. Then samples were taken before and after session.

2.1. Sampling

Samples were collected from AV fistula into tubes at room temperature and centrifuged within 1 hour. The serum was stored at -70°C prior to analysis.

2.2. Methods

- Blood Urea.
- Serum Creatinine: (modified rate Jaffe method).
- Complete blood count.
- Total Serum Calcium was measured according to Arsenazo Method (Farrell, 1984).
- Serum inorganic phosphorus was measured by phosphomolybdate complex method (Fraser et al, 1987).
- Serum sodium and potassium were measured.
- Human parathyroid hormone (hPTH):

The DIA source hPTH-EASIA (DIA source hPTH-EASIA Kit, Rue du Bosquet, Belgium), is a solid phase Enzyme Amplified Sensitivity Immunoassay performed on microtiter plates. Calibrators and samples react with the capture polyclonal antibodies (PAb, goat anti 1-34 PTH fragment) coated on microtiter well. After incubation, the excess of antigen is removed by washing.

- Then monoclonal antibodies (MAb, mouse anti 44-68 PTH fragment) labeled with horseradish peroxidase (HRP) are added. After an incubation period allowing the formation of a sandwich, the microtiter plate is washed to remove unbound enzyme labelled antibody. Bound enzyme-labelled antibody is measured through a chromogenic reaction.
- The chromogenic solution (TMB) is added and incubated. The reaction is stopped with the addition of Stop Solution and the microtiter plate is then read at the appropriate wavelength. The amount of substrate turnover is determined colourimetrically by measuring the absorbance, which is proportional to the PTH concentration.
- A calibration curve is plotted and PTH concentration in samples is determined by interpolation from the calibration curve.
- Serum Albumin was assayed according to Bromocresol Green Method (Burtis and Ashwood, 1986).

2.2.1. Statistical Methodology

The data collected were tabulated & analyzed by SPSS (statistical package for the social science software) statistical package version 20 on IBM compatible computer.

Qualitative data were expressed in number (No), percentage (%) and Quantitative data were expressed as mean & standard deviation (X ± SD) and analyzed by applying student t test for comparison of two groups of normally distributed data and two groups of not normally distributed data Mann-Whitney Test.

For comparison between the normally distributed quantitative data at interval for the same group paired samples t test was applied while for not normally distributed data by applying Wilcoxon Signed Test.

Pearson correlation was used for normally distributed quantitative variables, while Spearman correlation was used for not normally distributed quantitative variables or when one of the variables is qualitative.

Table 1. Sociodemographic characteristics of the studied patients

Sociodemographic characteristics:	Value **(n = 40)**	
Age (years):		
Range	46.50 - 66.00	
Mean ± SD	51.69 ± 3.73	
Gender:	NO.	%
Male	20	50.0
female	20	50.0

3. Results

Sociodemographic characteristics of the studied patients are shown in Table 1 and Table 2. There were highly significant decreases in predialysis BUN, sodium, and potassium at the end of the 1-month after the use of high-flux filters (Table 4). The predialysis values reflected the real patient status rather than immediate postdialysis values reflecting the permeability coefficient of the dialyzer membrane.

Table 2. Distributions of patients according to cause of ESRD

CAUSE	Frequency	%
DM	15	37.5
Hypertension	12	30
Glomerulonephritis	6	15
Obstructive uropathy	4	10
Polycystic kidney	3	7.5

ESRD indicates end-stage renal disease and DM indicates diabetes mellitus

Table 3. Comparison between predialysis and postdialysis mean arterial blood pressure for patients with low flux and high flux dialysis membranes

Mean arterial blood pressure	Predialysis (mean ± SD)	Postdialysis (mean ± SD)	Paired samples T test	P value
Low flux **(n = 40)**	111.63 ± 8.00	109.01 ± 7.01	1.89	0.06 NS
High flux **(n = 40)**	107.8 ± 8.14	103.30 ± 4.37	3.08	0.002 S

Table 4. Comparison between predialysis PTH, serum electrolytes, creatinine, Albumin, BUN and Haemoglobin for patients with low flux and high flux dialysis membranes

PTH, serum electrolytes, creatinine, Albumin, BUN and Hg	Dialysis membrane		Test of significance	P value
	Low flux (n = 40)	High flux (n = 40)		
PTH (pg/ml):				
Range	122.00 - 1223.00	92.00 - 1026.00	U = 3.15	0.002
Mean ± SD	415.96 ± 226.72	312.28 ± 191.98		S
Serum calcium (mg/dl):				
Range	7.50 - 11.30	7.50 - 11.00		0.79
Mean ± SD	8.49 ± 0.86	8.54 ± 0.85	t = 0.26	NS
Serum Phosphorus (mg/dl):				
Range	5.10 - 7.30	5.10 - 6.80		0.03
Mean ± SD	6.10 ± 0.44	5.90 ± 0.39	t = 2.12	S
BUN (mg/dl):				
Range	56.10 - 84.00	50.00 - 76.20		< 0.001
Mean ± SD	70.05 ± 7.04	63.00 ± 6.59	4.62	HS
Serum creatinine (g/dl):				
Range	8.00 - 11.20	8.00 - 10.70		0.04
Mean ± SD	9.60 ± 0.69	9.27 ± 0.68	2.08	S
Serum albumin (g/dl):				
Range	3.50 - 4.30	3.50 - 4.30		0.30
Mean ± SD	3.90 ± 0.19	3.85 ± 0.19	1.03	NS
Sodium (mmol/L)				
Range	137.00 - 147.00	135.00 - 145.20		< 0.001
Mean ± SD	143.04 ± 2.26	140.04 ± 2.57	5.53	HS
Potassium (mmol/L):				
Range	5.50 - 6.50	5.40 - 6.20		0.001
Mean ± SD	6.00 ± 0.26	5.80 ± 0.24	3.50	HS
Haemoglobin(g/dl):				
Range	7.60 - 12.30	8.50 - 12.70		0.001
Mean ± SD	9.50 ± 1.08	10.29 ± 1.04	t = 3.31	HS

(t): Student t test
(U): Mann-Whitney Test
PTH: Parathyroid Hormone
BUN: Blood Urea Nitrogen

Table 5. Comparison between predialysis and postdialysis PTH, serum electrolytes, creatinine, Albumin and BUN for patients with low flux and high flux dialysis membranes

PTH, serum electrolytes, creatinine, Albumin and BUN Low flux (n = 40) High flux (n = 40)	Predialysis (mean ± SD)	Postdialysis (mean ± SD)	Paired samples t test	P value
PTH (pg/ml):				
Low flux (n=40)	415.96 ± 226.72	405.75 ± 224.73	0.20	0.84 NS
High flux(n=40)	312.28 ± 191.98	216.60 ± 159.92	5.49	< 0.001 HS
Serum calcium (mg/dl):				
Low flux	8.49 ± 0.86	8.54 ± 0.84	2.07	0.04 S
High flux	8.54 ± 0.85	8.58 ± 0.87	2.21	0.03 S
Serum Phosphorus (mg/dl):				
Low flux	6.10 ± 0.44	5.90 ± 0.42	2.08	0.04 S
High flux	5.90 ± 0.39	3.80 ± 0.36	138.23	< 0.001 HS
BUN (mg/dl):				
Low flux	70.05 ± 7.04	66.98 ± 2.26	2.63	0.01 S
High flux	63.00 ± 6.59	21.28 ± 2.30	60.04	< 0.001 HS
Serum creatinine (g/dl):				
Low flux	9.60 ± 0.69	9.06 ± 1.54	2.02	0.04 S
High flux	9.27 ± 0.68	3.69 ± 0.28	72.76	< 0.001 HS
Serum albumin (g/dl):				
Low flux	3.89 ± 0.19	3.87 ± 0.18	0.48	0.63 NS
High flux	3.85 ± 0.19	3.80 ± 0.15	1.31	0.19 NS
Sodium (mmol/L)				
Low flux	143.04 ± 2.26	141.95 ± 2.11	2.23	0.02 S
High flux	140.04 ± 2.57	137.02 ± 1.79	11.61	< 0.001 HS
Potassium (mmol/L):				
Low flux	6.00 ± 0.26	5.88 ± 0.17	2.44	0.01 S
High flux	5.80 ± 0.24	4.09 ± 0.16	74.12	< 0.001 HS

Although creatinine was efficiently removed by both filter types, still there was a significant decline of predialysis serum creatinine at the end of the 1 month after the use high-flux filter (P = 0.04). On the other hand, there was no significant change in predialysis values of serum albumin or serum calcium after using high-flux filters (Table 4). The mean post dialysis levels of serum calcium were significantly higher than the predialysis levels for both low-flux and high-flux filters (post dialysis levels, 8.54 ± 0.84 mg/dL and 8.58 ± 0.87 mg/ dL, respectively). The mean post dialysis level of serum phosphorus showed a significant decline than the predialysis levels in low-flux filters and a highly significant decline than predialysis level in high flux ones (post dialysis levels, 5.90 ± 0.42 mg/dL and 3.80 ± 0.36 mg/dL, respectively) (Table 5).

At the end of the 1-month use of high-flux filters, predialysis intact PTH level showed a significant decline (P = 0.002) compared to the predialysis level using low-flux filters at the start of the study (312.28 ± 191.98 pg/ml versus 415.96 ± 226.72 pg/ml, respectively;) (Figure1). Post dialysis levels of intact PTH showed a highly significant decline than predialysis level after use of high-flux filter but not after the use of the low-flux one (Figure 2 and Figure 3).

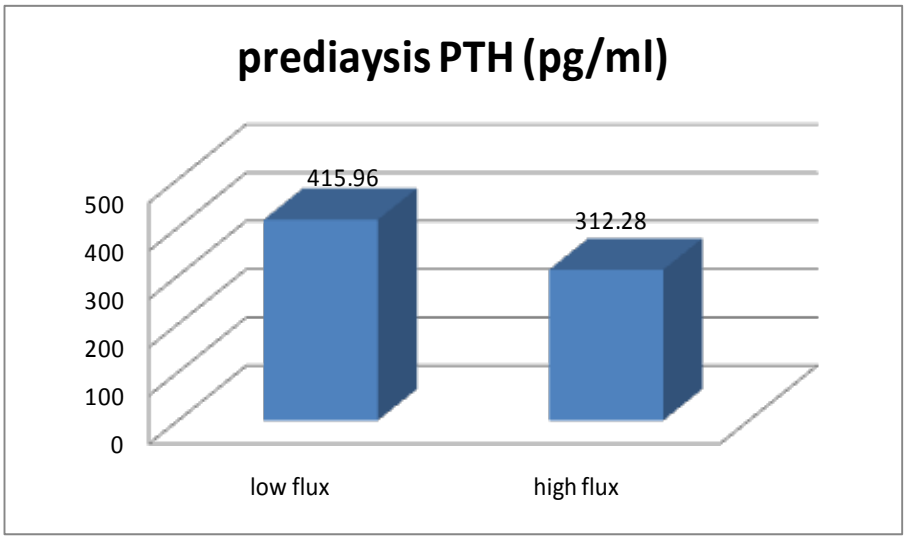

Figure 1. Comparison between predialysis PTH for patients with low flux and high flux dialysis membranes

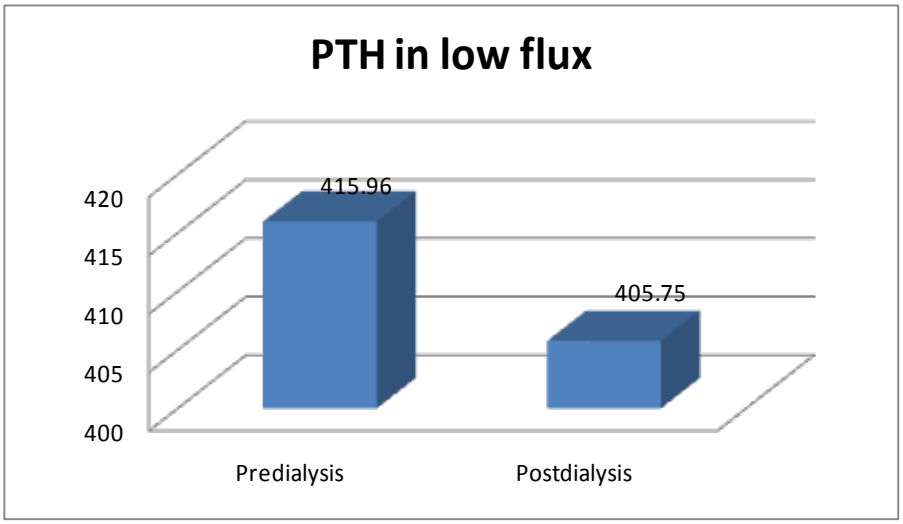

Figure 2. Comparison between predialysis and postdialysis PTH for patients with low flux dialysis membranes

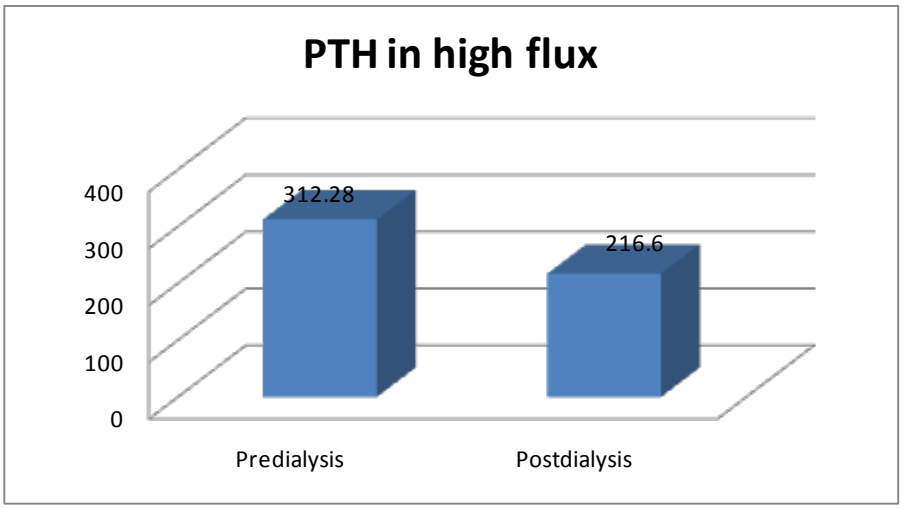

Figure 3. Comparison between predialysis and postdialysis PTH for patients with High flux dialysis membranes

It was found that predialysis intact PTH level correlated negatively with levels of predialysis serum calcium and positively with predialysis phosphorus levels while using low-flux filter, but not after switching to high-flux filter(Table 6, Table 7).

Table 6. Correlation coefficient (r) between Serum intact parathyroid hormone and predialysis serum electrolytes, BUN, serum creatinine and albumin levels on low-flux dialysis membrane

Predialysis iPTH versus predialysis serum electrolytes, BUN, serum creatinine and albumin	low-flux dialysis membrane	
	r	P value
Serum calcium (mg/dl)	-0.40	0.01 S
Serum Phosphorus (mg/dl)	0.55	< 0.001 HS
Sodium (mmol/L)	-0.07	0.64 NS
Potassium (mmol/L)	0.22	0.15 NS
BUN (mg/dl)	-0.01	0.93 NS
Serum creatinine (g/dl)	-0.36	0.02 S
Serum albumin (g/dl)	-0.20	0.21 NS

Table 7. Correlation coefficient (r) between Serum intact parathyroid hormone and predialysis serum electrolytes, BUN, serum creatinine and albumin levels on high-flux dialysis membrane

Predialysis iPTH versus predialysis serum electrolytes, BUN, serum creatinine and albumin	high-flux dialysis membrane	
	r	P value
Serum calcium (mg/dl)	- 0.01	0.37 NS
Serum Phosphorus (mg/dl)	0.55	0.11 NS
Sodium (mmol/L)	0.03	0.81 NS
Potassium (mmol/L)	0.19	0.23 NS
BUN (mg/dl)	0.06	0.71 NS
Serum creatinine (g/dl)	- 0.42	0.007 S
Serum albumin (g/dl)	- 0.11	0.48 NS

4. Discussion

Parathyroid hormone is a middle sized molecule with molecular weight 9500 Da [10]. Hyperparathyroidism is a common finding in patients with renal insufficiency. Calcitriol deficiency and phosphate retention together with hypocalcaemia are main factors involved in pathogenesis of secondary hyperparathyroidism [6].

In our study we found postdialysis highly significant decline of intact PTH after the use of high flux membranes, but not after the use of low flux ones. Also at the end of the 1-month use of high-flux filters, predialysis intact PTH level showed a significant decline compared to the predialysis level using low-flux filters at the start of the study.

In a study by Makar et al (2010), on 44 pediatric hemodialysis patients switched from low flux dialysis to high flux dialysis for 3 months, postdialysis levels of intact PTH were significantly lower than predialysis levels after use of high flux filter but not after the use of the low flux one [13].

At end of 3 months of use of high flux filters in study of Makar et al (2010), predialysis intact PTH level showed a highly significant decline compared to the predialysis intact PTH with low flux membranes at the start of the study [13].

In a study by Balducci et al (2004), different PTH behavior during hemodialysis with different types of dialysis membranes in 12 adult dialysis patients with secondary hyperparathyroidism. Each HD modality lasted 2 weeks for study period of 6 weeks. The first treatment consisted of standard bicarbonate dialysis with low flux polysulfone, followed by acetate-free biofiltration with high-flux-polysulfone or with polyacrylonitrile-AN69. Intact parathyroid hormone was assayed on the blood and dialysate samples to calculate iPTH adsorption. The results showed that polyacrylonitrile-AN69 and high-flux polysulfone induce a significantly larger drop in PTH serum levels as compared with low-flux-polysulfone, particularly in the first half of the dialysis session [12].

There was no significant change of serum albumin after the use of high-flux filters. According to Vanholder and colleagues, middle-sized molecules were defined as any solute with molecular weights between 500 Da and 40 000 Da [14]. Albumin, with a molecular weight of 65 000 Da, is considered a relatively large molecule to be filtered by both membrane types. Another possible explanation is hepatic overproduction or decrease anorexic agents with amelioration of appetite.

Krieter and Canaud found that highly permeable membranes may increase albumin loss and lead to harmful consequences; however, they could not estimate accurately the extent of albumin loss through highly permeable dialysis membranes [15].

Lindsay and Spanner noted that switching from low-flux to high-flux dialysis membranes did not increase the protein catabolic rate as previously found through using some high-flux membranes as the AN69 dialyzer [16] instead; a significant increase in predialysis serum albumin levels was observed [17].

It was further postulated that this may be the result of improved dietary intake and potential explanation involving the removal of plasma substances that inhibit appetite, such as the putative factor in uremic plasma, leptin (16kD), and other peptides [18].

However, in the study of Makar et al, there was no significant change of serum albumin after use of high flux filters [13]. Also, in a study by Ayli et al, there was no statistical significant difference between low and high flux groups as regard albumin level [19].

In the present study, there was a highly significant decline of serum sodium, potassium, creatinine, and BUN levels after the use of high flux filters. Although they were significantly removed by low flux filters for being water soluble and with small molecular weight (eg, urea is 60 Da), still they were more efficiently eliminated by the use of increasingly permeable high-flux dialysis membranes with excellent blood purification. High-flux filters with large pore sizes are efficient in removal of toxins with medium weight, but on the other hand, other smaller substances may be markedly decreased [15].

In our study mean arterial blood pressure declined significantly after the use of high-flux membranes,but not after the use of low-flux ones and this may be related to significant ultrafiltration occurred with high flux dialyzers.

In a study by Li Y et al, on thirty patients undergoing dialysis for at least 2 years with a low-flux dialyzer were switched to the FX60 dialyzer for 3 years, the mean arterial blood pressure decreased significantly after the switch to high flux dialysis membranes [20].

In prospective crossover study was performed by Takenaka et al, in 10 adult HD patients with low-flux and high-flux dialyzers the mean blood pressure remained unchanged in either state [22].

In our study there was no statistical significant difference between use of low flux dialysis and high flux dialysis as regard serum calcium but there was a highly significant reduction in phosphorus level.

In a study by Ayli et al, there was no statistical significant difference between the high flux dialyzer group and low flux group as regard Ca but there was significant reduction in P level [19].

In study of Makar et al, there was no statistical significant difference between use of low flux dialysis and high flux dialysis as regard Ca but there was statistical significant decrease in serum P and ALP after use of high flux dialysis compared to low flux dialysis [13].

In our study there was a highly significant increase in the mean of hemoglobin levels from 9.50 ± 1.08 to 10.29 ± 1.04 after one month of use of high flux dialysis (P-value: 0.001). However, in a study by Locatelli et al, on 84 adult HD patients, they found that the hemoglobin levels increased non significantly from 9.5 ± 0.8 to 9.8 ± 1.3 g/dl in the population as a whole, with no significant difference between the low and high flux groups (P = 0.485) [23]. Also a study by Schneider et al, after 52 weeks, the low-flux and the high-flux groups did not differ with respect to hemoglobin (P = 0.62) [24].

The increase in Hb level in our study may be attributed to potential benefits of high flux membranes in reduction of erythropoietin resistance [25]. This might be related to reduction in the level of PTH among these patients as hyperparathyroidism is usually listed as one of possible reasons for impaired response to recombinant human erythropoietin (rHuEPO) in patients with renal disease [26].

On the other hand PTH could interfere with endogenous erythropoietin production [27]. PTH also enhances entry of calcium into RBC, stimulates their Ca ATPase and increases osmotic fragility of RBC and decreases their life span [28].

We found that intact PTH correlated negatively with serum calcium and positively with phosphorus only in predialysis samples with the use of low flux and not high flux filters. While there is an established relationship between calcium, phosphorus, and intact PTH, this was not found when using high flux membranes, denoting that PTH, being a middle-sized molecule, was not only influenced by the level of calcium and phosphorus, but also rather removed directly through the larger pores of high flux membranes.

5. Conclusion

High-flux dialysis membranes are more efficient than low-flux membranes in removal of PTH, which is one of the middle-sized uremic toxins, and they might help in minimizing the consequences of bone disease associated with hyperparathyroidism in patients with ESRD.

Recommendation

It is recommended to use high–flux dialysis membranes for H.D patients with secondary hyperparathyroidism.

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