

Effect of High-flux Versus Low-flux Dialysis Membranes on Parathyroid Hormone

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Introduction. 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. The aim of this study was to investigate the influence of permeability of low-flux versus high-flux dialysis membranes on intact PTH during hemodialysis in children.

Materials and Methods. Forty-four children aged between 4 and 13 years old 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 3 months. Serum electrolytes and intact PTH before and after dialysis were compared before and after changes in dialysis membrane.

Results. At the end of the 3-month use of high-flux filters, predialysis intact PTH level (49.40 ± 19.64 ng/dL) showed a highly significant decline ($P < .001$) compared to the predialysis intact PTH (21.67 ± 4.85 ng/dL) with low-flux membranes at the start of the study. Intact PTH level correlated negatively with serum ionized calcium and positively with serum phosphorus levels only in the predialysis samples with the use of low-flux but not high-flux filters.

Conclusions. In children, high-flux dialysis membranes are more efficient in removal of intact PTH, one of the middle-sized uremic toxins, than low-flux membranes.

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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).²

Quality of life in ESRD patients on dialysis is also dependent on the quality of dialysis. Three general types of membrane 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 There is increasing evidence that all cause-specific mortality and hospitalization rates are lower for hemodialysis patients treated with specific membranes compared with those for patients on dialysis with cellulose membranes.⁴ The choice of a dialysis membrane should take into account the following⁵: 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. For conventional dialysis, low-flux membranes are suitable, but to achieve hemofiltration or hemodiafiltration high-flux membranes are necessary. In the general practice guidelines for hemodialysis in children, justification for the use of high-flux synthetic membranes, as used in on-line hemodiafiltration, remains a matter of debate in pediatric dialysis for short periods only while waiting for their kidney transplant.⁶ In the developing countries such as Egypt, children may stay for longer durations on hemodialysis to be transplanted, and hence, the validity of using such high-flux filters could be more appropriate.

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 β 2-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.^{10,14} In fact, not only low-flux membranes do not remove middle-sized molecule toxin, but also the concentrations of these compounds actually tend to increase during standard dialysis due to hemoconcentration as a consequence of the extraction of the extra fluid accumulated in the body between dialysis sessions.²² On the other hand, highly permeable membranes are efficient in removal of both small non-protein-bound and middle-sized uremic toxins, and thus, helpful in maintenance of residual kidney function and reduction of malnutrition and mortality.^{5,19}

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.⁸ 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.⁹ Changes in

PTH during hemodialysis have been explained by the influence of ionized calcium changes on PTH secretion. Parathyroid hormone changes during hemodialysis are dependent not only on the increase in calcium, but also on the nature of the dialysis membrane.⁹ Parathyroid hormone in patients with kidney failure is affected by ionized calcium and dialysis membrane and also by the use of calcium-containing phosphate binders and vitamin D analogues. Both of these agents have been shown to suppress PTH release and improve the related bone disease.¹¹

The aim of this study was to investigate the influence of permeability of low-flux versus high-flux hemodialysis membranes on PTH during hemodialysis in children.

MATERIALS AND METHODS

Patients

Forty-four pediatric patients with ESRD who were on regular hemodialysis in the Center of Pediatric Nephrology and Transplantation of Cairo University Children's Hospital were enrolled in a prospective study. They were 22 girls and 22 boys. The study was conducted through a 3 months' duration from August 2008 to November 2008. Inclusion criteria were pediatric age (≤ 13 years) when diagnosed with ESRD (glomerular filtration rate, < 15 mL/min/1.73 m²) and minimum dialysis duration of 6 months. All patients were on 3-hour sessions of dialysis, 3 times per week using Fresenius 4008B hemodialysis machine and single-use low-flux polysulfone filters (Fresenius F3, F4, and F5, according to patients' surface area) and pediatric lines using sodium bicarbonate base and heparin as anticoagulant. Patients with acute kidney injury or with unsatisfactory vascular access affecting dialysis adequacy were excluded from the study. The study protocol was approved by the local ethics committee, and informed written consent was obtained from the patients or their parents.

Sampling Procedure

At the start of the study, while the patients were on the conventional low-flux filters, a baseline predialysis arterial sample and a postdialysis venous sample were obtained, and laboratory investigations were measured including urea, creatinine, sodium, potassium, ionized calcium, phosphorus, alkaline phosphatase, albumin, and

intact PTH. All of the patients were switched to high-flux polysulfone filters (Fresenius F40 or F50, proportionately to their initial low-flux filters surface areas) for 3 months duration without changing any of the other dialysis prescription parameters (except for ultrafiltration to reach their ideal dry weight as needed). Moreover, the doses of vitamin D analogues or phosphate binders were kept constant through the study. At the end of the 3 months, the same investigations were repeated before and after dialysis.

Hemodialysis

Hemodialysis machines with volumetric control (Fresenius Medical Care 4008B and 4008S, Homburg, Germany) were used. The standard dialysis bath consisted of sodium, 140 mEq/L; potassium, 2 mEq/L; calcium, 3 mEq/L; and bicarbonate, 35 mEq/L. The ultrafiltration rate was programmed to reach the patient's optimal dry weight defined as the postdialysis body weight below which the patients developed symptomatic hypotension or muscle cramps in the absence of edema. Heparin was used for anticoagulation.

Parathyroid Hormone

Samples were collected into heparinized tubes at room temperature and centrifuged within 1 hour. The plasma was stored at -20°C prior to analysis. Plasma intact PTH was measured by immunoradiometric assay using Elecsys 2010 autoanalyzer system (Roche Diagnostics, Basel, Switzerland) with a reference range of 1.2 ng/dL to 7.2 ng/dL.

Ionized Calcium

Samples were collected into heparinized tubes at room temperature, centrifuged within 15 minutes, and the plasma was analyzed for ionized calcium within 30 minutes using Nova SST, stat profile 9 (Nova Biomedical, Waltham, Massachusetts, USA).

Other Serum Parameters

Serum sample for measurement of other parameters were collected at room temperature and centrifuged within 1 hour. The serum was stored at -20°C prior to analysis using Synchron cx5 autoanalyzer (Beckman, USA). The reference range was 135 mmol/L to 148 mmol/L for sodium, 3.5 mmol/L to 5.3 mmol/L for potassium, 4 mg/dL to 7 mg/dL for phosphorus, 50 IU/L to 644 IU/L for

alkaline phosphatase, and 3 mg/dL to 4.8 mg/dL for albumin. After obtaining informed written consent, all samples were withdrawn during the routine 3-monthly blood sampling according to the standard protocols to assess dialysis adequacy (KT/V), anemia, and ionized calcium and phosphorus levels, in order to minimize blood sampling.

Statistical Analyses

Quantitative data were presented as mean \pm standard deviation values. The SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA) was used for analyses. The Pearson correlation coefficient was used to determine significant correlations between quantitative data. Qualitative data were presented as frequencies and percentages. The paired *t* test was used to study the changes in parameters after dialysis and after changing membranes into high flux. The significance level was set at *P* values less than .05.

RESULTS

Characteristics of patients are shown in Table 1. There was no significant change in the equilibrated KT/V after the use of high-flux filter (1.56 ± 0.33 versus 1.56 ± 0.29 ; *P* = .61). There were highly

Table 1. Characteristics of Patients*

| Characteristics | Value |
|----------------------------|---------------------------|
| Number of patients | 44 |
| Mean age, y | 10.7 \pm 2.78 (4 to 13) |
| Gender | |
| Male | 22 (50) |
| Female | 22 (50) |
| Mean dialysis duration, y | 3.34 \pm 1.02 (2 to 6) |
| ESRD cause | |
| Unknown | 14 (31.8) |
| Posterior urethral valve | 4 (9.0) |
| Reflux nephropathy | 4 (9.0) |
| Nephronophthisis | 3 (6.8) |
| Urinary calculi | 3 (6.8) |
| Cystinosis | 3 (6.8) |
| CIN | 2 (4.5) |
| Bardet-Biedl syndrome | 2 (4.5) |
| FSGS | 2 (4.5) |
| Other GN lesions | 2 (4.5) |
| Traumatic urethral rupture | 1 (2.7) |
| Others | 4 (9.0) |

*Values in parentheses are percents for frequencies and range for mean values. ESRD indicates end-stage renal disease; CIN, chronic interstitial nephritis; FSGS, focal segmental glomerular sclerosis; and GN, glomerulonephritis.

Table 2. Mean Predialysis Values for Patients With Low-flux and High-flux Dialysis Membranes

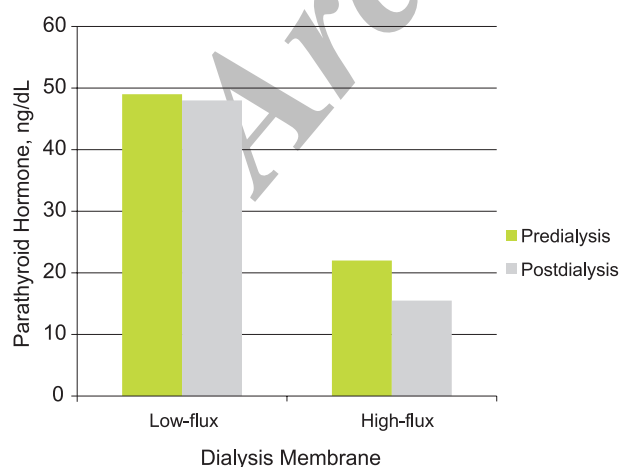
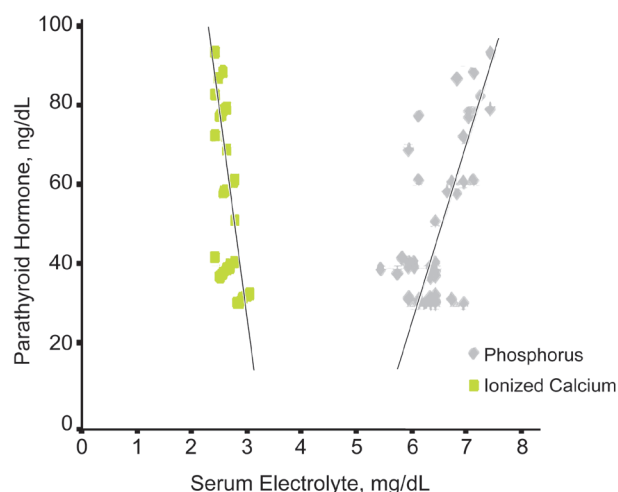
| Parameter | Dialysis Membrane | | P |
|----------------------------|-------------------|---------------|--------|
| | Low-flux | High-flux | |
| Albumin, mg/dL | 3.17 ± 0.18 | 3.12 ± 0.12 | .15 |
| Urea, mg/dL | 151.20 ± 12.18 | 138.60 ± 8.20 | < .001 |
| Creatinine, mg/dL | 8.97 ± 0.42 | 8.70 ± 0.46 | .002 |
| Sodium, mmol/L | 143.84 ± 4.08 | 140.36 ± 2.36 | < .001 |
| Potassium, mmol/L | 5.75 ± 0.57 | 5.50 ± 0.28 | < .001 |
| Calcium, mg/dL | 3.93 ± 0.44 | 3.87 ± 0.35 | .48 |
| Phosphorus, mg/dL | 6.75 ± 0.26 | 6.42 ± 0.47 | < .001 |
| Alkaline phosphatase, IU/L | 567.7 ± 85.2 | 478.3 ± 130.4 | < .001 |

significant decreases in predialysis serum urea, creatinine, phosphorus, alkaline phosphatase, sodium, and potassium at the end of the 3 months after the use of high-flux filters (Table 2). The predialysis values reflected the real patient status rather than immediate postdialysis values reflecting the permeability coefficient of the dialyzer membrane. Although creatinine was efficiently removed by both filter types, still there was a significant decline of predialysis serum creatinine at the end of the 3 months after the use high-flux filter ($P = .002$). On the other hand, there was no significant change in serum albumin or ionized calcium of predialysis values after using high-flux filters (Table 2).

The mean postdialysis levels of ionized calcium were significantly lower than the predialysis levels for both low-flux and high-flux filters (postdialysis levels, 3.74 ± 0.22 mg/dL and 3.70 ± 0.31 mg/dL, respectively). The mean postdialysis levels of serum phosphorus were significantly lower than the predialysis levels in both low-flux and high-

flux filters (postdialysis levels, 4.81 ± 0.52 mg/dL and 4.10 ± 0.12 mg/dL, respectively). Also, postdialysis levels of serum alkaline phosphatase were significantly lower than the predialysis levels after use of high-flux filter (postdialysis level, 425.06 ± 124.52 mg/dL) but not after low-flux use (postdialysis level, 483.52 ± 105.87 mg/dL).

At the end of the 3-month use of high-flux filters, predialysis intact PTH level showed a highly significant decline ($P < .001$) compared to the predialysis level using low-flux filters at the start of the study (21.67 ± 4.85 ng/dL versus 49.40 ± 19.64 ng/dL, respectively; Figure 1). 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. It was found that predialysis intact PTH level correlated negatively with levels of predialysis ionized calcium and positively with predialysis phosphorus levels while using low-flux filter (Figure 2), but not after switching to high-flux filter.

**Figure 1.** Mean predialysis and postdialysis intact parathyroid hormone values after treatment with low-flux and high-flux dialysis membranes.**Figure 2.** Correlation between serum intact parathyroid hormone and predialysis serum levels of ionized calcium and phosphorus on low-flux dialysis membrane.

DISCUSSION

Parathyroid hormone is a middle-sized molecule with a molecular weight of 9225 Da.¹⁵ It has been proposed that the markedly elevated levels of PTH in uremia may represent a “uremic toxin” responsible for many of the abnormalities of the uremic state and bone disease.^{12,16} We found a highly significant decline of intact PTH at the end of 3-month use of high-flux filters for children on hemodialysis. Such a decline in PTH was observed without significant difference in the KT/V between low-flux and high-flux filters. Highly permeable dialysis membranes with large pore size are more efficient in removal of middle-sized molecules of uremic toxins than dialysis membranes with small pore size.^{5,17}

We observed that postdialysis intact PTH declined significantly after the use of high-flux membranes, but not after the use of low-flux ones. This is supported by the decline in postdialysis serum alkaline phosphatase after the use of high-flux membranes. Grant and colleagues found that ionized calcium was the major stimulus to PTH release.¹⁸ On the other hand, high serum phosphorus level is another stimulus to PTH release.⁸ Silver and Levi found that small decreases in serum calcium and more prolonged increases in serum phosphate stimulated the parathyroid glands to secrete PTH.²⁰ On the other hand, Abbott and coworkers found that the available data were inconsistent with the view that the set point for calcium-regulated PTH release was abnormal in secondary hyperparathyroidism. They found that some patients exhibited elevated PTH despite elevated calcium levels. This functional dysregulation was thought to result from downregulation of calcium-sensing receptor expression associated with parathyroid hyperplasia, particularly if nodular.²¹

In this study, postdialysis level of ionized calcium was significantly lower than its predialysis level. This may be attributed to metabolic alkalosis induced by the use of bicarbonate dialysate irrespective of the type of dialysis membrane. Kirschbaum reported that high bicarbonate hemodialysis was associated with low phosphorus level, but it was not associated with the significant changes of ionized calcium.¹³ The use of low-calcium dialysate is another factor that could explain the decline in postdialysis levels of ionized calcium.

During dialysis with a high-calcium dialysate, PTH levels fall, mainly as a result of suppression

of parathyroid activity by calcium. Removal of PTH across the dialysis membrane is of minor significance. In contrast, when using dialysis fluid with physiological or low-calcium concentration, parathyroid suppression no longer occurs. Any fall in plasma calcium as a result of low-calcium dialysate will lead to an increase in PTH secretion for the duration of dialysis.¹²

We found that intact PTH correlated negatively with ionized 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.

In this study, there was a highly significant decline of serum sodium, potassium, phosphorus, and urea levels after the use of high-flux filters. Although they were efficiently 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.⁷

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.⁷ 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 dialyzer²³; instead, a significant

increase in predialysis serum albumin levels was observed.²⁴ 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 (16 kD), and other peptides.^{25,26}

CONCLUSIONS

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

CONFLICT OF INTEREST

None declared.

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