Original Paper

Plasma Beta-Trace Protein as a Marker of Residual Renal Function: The Effect of Different Hemodialysis Modalities and Intra-Individual Variability over Time

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Key Words

Beta-trace protein • GFR estimation • Hemodiafiltration • Hemodialysis • Peritoneal dialysis • Residual renal function

Abstract

Background/Aims: Beta-trace protein (BTP) is a low-molecular-weight molecule, which may be used to assess residual renal function (RRF) in dialysis patients. Here we evaluated the influence of hemodialysis (HD) and hemodiafiltration (HDF) on plasma BTP, and analyzed the inter- and intra-individual variability of plasma BTP over time in HD and peritoneal dialysis (PD) patients. **Methods:** In 12 prevalent HD patients, the effect of a single session of low-flux HD, high-flux HD and HDF on plasma BTP was studied. Blood samples were taken at baseline, after 120 and 240 minutes, and at the start of the next dialysis session. In 13 HD patients and 10 PD patients, inter- and intra-individual variability over three months was studied (monthly and weekly, respectively). Plasma BTP was measured using a nephelometric method. **Results:** No significant decrease in plasma BTP was seen following a session of low-flux HD. Both high-flux HD and HDF resulted in a significant decrease immediately after dialysis (22% and 61% median decrease, respectively). A significant reduction of the molecule persisted only in HDF and a significant decrease (-15%) was still found immediately before the start of the next dialysis session. In both HD and PD patients, the reproducibility over time was excellent with intra-class correlation coefficient of 0.96 (0.93-0.99) and 0.92 (0.86-0.99) respectively. In a small cohort of PD patients, fair agreement existed between mGFR (average of renal urea and creatinine clearance from a 24 hours urine collection) and the BTP-based GFR estimation.

Conclusion: BTP is a stable marker and a promising tool for RRF estimations in PD and HD patients. In patients receiving HDF, plasma levels of BTP should be interpreted with caution.

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Introduction

In patients undergoing hemodialysis (HD), the residual native kidney function, also known as residual renal function (RRF), is a potent predictor of improved survival [1, 2] as well as of quality of life as RRF influences fluid balance, food intake and diet [3]. Given its clinical relevance, current guidelines recommend to routinely measure RRF and to adopt measures for preserving it [4, 5]. As such, RRF is an important part of the dialysis patient's assessment and can be important in adjusting the dialysis regimen [6]. Unfortunately, accurate determination of RRF remains a diagnostic challenge. Inulin clearance with urinary sampling is widely regarded as the gold standard for measuring glomerular filtration rate (GFR). However, it requires a continuous intravenous infusion, several blood sampling moments and timed urine collections [7]. Therefore, alternative methods including plasma and urinary clearance of other exogenously added substances, such as iothexol, have been proposed, as sampling for plasma iothexol clearance calculations can be minimized to two time points [8-10]. Another alternative for inulin clearance is to calculate the average of urea- and creatinine clearance, but this technique is also rather cumbersome [11]. Indeed, RRF may vary over the interdialytic period in patients undergoing HD, and the urine collection should be made over the entire interdialytic interval (usually two days) [4].

Beta-trace protein (BTP) is a low-molecular-weight (LMW) protein emerging as a novel endogenous GFR marker and holds promise as a tool for the assessment of RRF in HD patients without the need for urine collections [12]. BTP, also known as prostaglandin D2 synthase (PGDS), is a glycoprotein with a molecular mass of 23-29 kDa. With decreasing renal function, BTP plasma levels rise [13, 14] and virtually all BTP appears to be freely filtered through the glomerulus – whether this is followed by tubular reabsorption and degradation or not requires further study [12, 15]. Different BTP-based equations were proposed to translate plasma BTP levels to estimated GFR in different non-dialysis populations [16-18] and, more recently, in dialysis patients (i.e. BTP alone [19] or in combination with other serum proteins [20]). In the specific context of HD, BTP-based GFR estimations could offer advantages over cystatin-C and β -2 microglobulin, other LMW proteins (respectively 13.3 kDa and 11.8 kDa) used as endogenous GFR markers [19]. Indeed, due to its larger size, it can be expected that blood levels of BTP are not, or less, affected by the dialysis process itself. According to the study of Gerhardt *et al.* [21], plasma BTP level does not change significantly following a HD session, either with a low-flux or high-flux membrane [21, 22]. Increasing use of convective therapies, such as hemodiafiltration (HDF), however, prompts to further study the BTP dynamics in different dialysis modalities. Moreover, in assessing the validity of a diagnostic biomarker, it is important to understand the degree to which measurements from a single sampling moment are representative of levels over a longer time period for a given subject. The objective of this study was to evaluate the influence of HDF and HD on plasma levels of BTP. In addition, intra-individual variability over three months was studied in prevalent dialysis patients. Furthermore, agreement of the recently proposed BTP-based GFR formula with measured GFR was assessed in a subgroup of patients.

Materials and Methods

Study population and design

To evaluate the effect of hemodialysis modality on BTP levels, 12 prevalent HD patients were asked to participate (Cohort 1). All subjects were subjected once only to three different dialysis sessions: HD with a low-flux membrane (PolyFlux 21L, Gambro), HD with a high-flux membrane (Polyflux 210H, Gambro) and predilution HDF (Polyflux 210H, Gambro). Blood samples were drawn immediately before the start of the

treatment (t_0), halfway through the session (t_1 , 120 minutes) and at the end of the session (t_2 , 240 minutes). To assess a more long-term effect, the next time point was defined as the start of the next dialysis session (t_3). All treatments were standardized to 4 hours and were preceded by at least one dialysis-free day. The three different dialysis modalities were separated by at least one week.

Intra-individual variability over time in HD patients was analyzed in 13 patients of the Mapping of Inflammatory Markers in Chronic Kidney Disease (MIMICK1) cohort (Cohort 2) with available serial samples. This cohort included adult patients on maintenance HD therapy recruited during the period of February 2004 - April 2004 in six dialysis units in Uppsala (Sweden). All patients were clinically stable. BTP levels were quantified at 4 different time points: baseline, 1, 2 and 3 months.

Similarly, 10 prevalent peritoneal dialysis (PD) patients with available weekly samples for a period of three months were chosen from a parallel cohort of clinically stable PD patients (MIMICK2, Cohort 3). The MIMICK2 cohort contains prevalent PD patients, recruited at the Karolinska University Hospital and Danderyds Hospital in the Stockholm region April 2009 - August 2010. Nine out of 10 patients were treated with continuous ambulatory PD and one patient received automated PD.

All studied patients were receiving dialysis for at least 3 months at the moment of inclusion. The Ethics Committee of the Karolinska Institutet (EPN) at the Campus Flemingsberg, Stockholm, Sweden, approved all study protocols. The study conformed to the principles outlined in the declaration of Helsinki. Written informed consent was obtained from all participants.

Blood sampling and treatment modalities

In *Cohort 1* and *Cohort 2*, baseline samples were taken immediately before dialysis. For *Cohort 1*, serial sampling was performed from the afferent sampling port without changing the blood flow. Correction for net ultrafiltration (UF) for the measurements taken during dialysis was done using the formula “corrected BTP = uncorrected BTP / (1 + Δ BW/0.2 BW)” where Δ BW is change in the bodyweight (BW) during dialysis, assuming linear UF [23]. For low-flux HD, mean net ultrafiltration (UF) was 3.1 liters, for high-flux HD 3.0 liters and for HDF 3.0 liters. The UF rate (0.74–0.77 liters/h) was similar during the three different sessions. The extracorporeal blood-flow (Q_b) was 250–330 ml/min and the dialysate flow rate (Q_d) was 500 ml/min; sodium and bicarbonate concentrations in the dialysate were 139 and 34 mmol/l, respectively. Anticoagulation was achieved with tinzaparin sodium (Innohep, Leo Pharma, Sweden) given at the start of the dialysis. In *Cohort 3*, venous blood samples were taken after an overnight fast, without interrupting the ongoing PD treatment.

Biochemical measurements

Heparin plasma samples were centrifuged within 30 minutes (2500g, 20 min, 4°C) and immediately stored at -80°C for later analysis. All samples from a given individual were run in the same batch. BTP levels were quantified using latex-enhanced immunonephelometry (N Latex BTP, Siemens) on the Konelab 20XT i analyzer (Thermo Scientific, Finland). Interassay coefficient of variation (CV) was 9.4%. According to the manufacturer, values $\leq$ 0.70 mg/L are reported to represent the lower 95% range of a healthy adult population.

GFR estimation and measurement

The recently proposed BTP-based GFR equation was used to estimate GFR in the patients of all three cohorts [$eGFR = 95 \times BTP^{-2.16} \times 1.652$ if male] [19] (Table 1). For this calculation, BTP levels of the first available samples of all studied subjects were used. BTP-based $eGFR$ for Cohort 1 and 2 are given for illustrative purposes. In *Cohort 3*, GFR was measured (mGFR) at baseline as the average of renal urea and creatinine clearance from a 24 hours urine collection in patients with a urine output of >250 ml a day (9 out of 10 PD patients). Median diuresis (IQR) was 1289 (630–1711) ml/24h and median mGFR was 3.4 (2.1–4.6) ml/min/1.73m².

Statistical analysis

Continuous data are expressed as median (interquartile range – IQR) or nominal data as percentage, as appropriate. Statistical significance was set at the level of $p < 0.05$. Comparisons between two groups were assessed with the non-parametric Wilcoxon test for continuous variables and Fischer exact test for nominal variables. Differences between three groups were analyzed by Kruskal Wallis test.

For evaluating the intra-individual variability over time, intraclass correlation coefficients (ICCs) and their 95% confidence intervals were calculated using a mixed effect model with batch and subject included as random effects (subject was nested within batch) and time as fixed effect ICCs ≥ 0.75 were considered to indicate excellent correlation, $0.4 \leq \text{ICCs} < 0.75$ were considered to be indicative of fair-to-good correlation, and ICCs ≤ 0.4 were indicative of poor reproducibility. Agreement of the BTP-based eGFR with mGFR was studied by Bland Altman analysis [24]. All analyses were performed using statistical software (*StataCorp. 2016. Stata Statistical Software: Release 15, College Station, TX: StataCorp LP*).

Results

Demographics

Baseline-descriptive characteristics of the study cohorts are presented in Table 1. Overall, median BTP levels were 11-15 fold above normal. The majority of the patients were men. No effect of BMI or sex was observed.

Effect of hemodialysis modality (Cohort 1)

Baseline creatinine, urea and BTP levels as well as technical characteristics of the three dialysis modalities are shown in Table 2. All variables were comparable between the three modalities. Table 3 shows BTP-values during the course of three sessions of different modalities, both uncorrected numbers and levels corrected for net ultrafiltration. When correction for ultrafiltration is applied, both high-flux HD and HDF resulted in a significant decrease immediately after dialysis (22% and 61% median decrease, respectively) (Table 3). Hemodiafiltration was the only modality with a prolonged effect on BTP-levels, with a median decrease immediately before the start of the next dialysis session of 15%.

Variability over time in patients receiving dialysis (Cohort 2 and 3)

Excellent reproducibility over time was shown for both HD and PD patients. ICC (95%CI) was 0.962 (0.928 – 0.995) and 0.923 (0.858 – 0.987), respectively. In line, Spearman correlation coefficients for paired measurements of BTP at baseline vs 3 months were high, respectively 0.982 for HD and 0.964 for PD. BTP-levels over time are depicted graphically in Fig. 1.

Table 1. Characteristics of the study cohorts. Variables are presented as median (IQR). BMI= body mass index; HD= hemodialysis; PD= peritoneal dialysis; BTP= beta-trace protein. According to Shafi et al, eGFR= $95 \times \text{BTP}^{-2.16} \times 1.652$ if male (ref 19)

	Cohort 1 (n=12)	Cohort 2 (n=13)	Cohort 3 (n=10)
Age (years)	55 (41 – 65)	71 (58 – 76)	63 (50 – 76)
Sex (M/F)	9/3	7/6	7/3
Body weight (kg)	62.5 (54.0 – 75.5)	73.5 (67.5 – 82.5)	70.3 (67.0 – 85.5)
BMI (kg/m ²)	22.0 (19.5 – 24.5)	27.0 (22.7 – 30.2)	24.8 (23.8 – 27.8)
Maintenance dialysis			
- low flux HD (%)	100	62	0
- high flux HD (%)	0	38	0
- PD	0	0	100
Dialysis vintage (months)	34 (23 – 64)	24 (14-33)	6 (5 – 10)
BTP baseline (mg/l)	10.7 (9.3 – 11.6)	8.3 (4.9 – 12.2)	7.7 (5.2 – 8.9)
BTP based eGFR (ml/min/1.73m ²)	0.9 (0.7 – 1.1)	1.5 (0.5 – 4.4)	1.9 (1.4 – 2.7)

Table 2. Baseline values and technical characteristics of the 3 dialysis modalities of Cohort 1. Variables are presented as median (IQR). URR= urea reduction rate; spKt/V= single pool Kt/V; eKt/V= equilibrated Kt/V

	Low-flux HD	High-flux HD	Hemodiafiltration	p-value
Creatinine (mg/dl)	10.74 (3.36)	9.88 (3.94)	9.79 (3.9)	0.74
Urea (mg/dl)	133 (58)	142 (59)	126 (63)	0.47
Baseline BTP (mg/l)	10.3 (1.9)	11.1 (2.2)	10.7 (3.1)	0.80
URR (%)	71.0 (12.9)	70.8 (10.9)	72.5 (8.7)	0.38
spKt/V	1.50 (0.66)	1.51 (0.58)	1.56 (0.50)	0.48
eKt/V	1.31 (0.54)	1.32 (0.48)	1.37 (0.42)	0.46

Table 3. Time course of plasma BTP concentration during the course of low-flux and high-flux HD and hemodiafiltration sessions. Variables are presented as median (IQR). BTP-levels were quantified at the start of dialysis (t_0), halfway through the session (t_1), at the end of the session (t_2) and immediately before the start of the next session (t_3)

	t_0	t_1	t_2	t_3	p-value
Uncorrected values					
Low-flux HD	10.3 (1.9)	10.8 (2.1)	12.3 (2.2)	11.1 (1.3)	0.003
High-flux HD	11.1 (2.2)	9.9 (2.4)	10.7 (2.1)	10.4 (1.8)	0.593
Hemodiafiltration	10.7 (3.1)	6.3 (2.1)	5.3 (1.8)	9.3 (1.4)	<0.001
Values after correction for net ultrafiltration					
Low-flux HD	10.3 (1.9)	9.4 (1.8)	9.8 (2.3)	11.1 (1.3)	0.044
High-flux HD	11.1 (2.2)	8.9 (2.1)	8.6 (2.0)	10.4 (1.8)	<0.001
Hemodiafiltration	10.7 (3.1)	5.6 (2.1)	4.4 (1.8)	9.3 (1.4)	<0.001

BTP-based formula for estimating GFR

Bias (mean difference) for the BTP-based eGFR was low, -0.74 ($\pm$ 1.41) ml/min/1.73m², with fair 95% limits of agreement (-3.51 to 2.02) (Fig. 2). In general, the equation underestimates the mGFR.

Discussion

The present study shows that the pre-analytical variability of BTP-levels in dialysis patients is related to treatment characteristics. Both high-flux HD and HDF result in a clearance of the BTP-molecule. However, the decrease in BTP-level is prolonged and still present immediately before the start of the next dialysis session only when HDF is applied. This finding underscores the importance of the clinical context for the interpretation of the novel BTP-based GFR estimations. In patients on maintenance therapy with HD or PD, BTP levels appear to be in a steady state, and the intra-individual variability over time is low. In conclusion, using plasma BTP-levels to estimate RRF without the necessity for urine collection might be an attractive option, at least in patients receiving HD or PD, but not HDF.

Hemodialysis, based on the diffusive transport of solutes across a semipermeable

Fig. 1. Variability over time of plasma BTP in prevalent HD (panel A) and PD (panel B) patients. Variability over 3 months in prevalent hemodialysis patients (Cohort 2) with monthly sampling and in prevalent peritoneal dialysis patients (Cohort 3) with weekly samples. Blue dots represent high-flux membranes, green triangles represent low-flux membranes.

membrane, is the most widely used renal replacement technique. HD with low-flux membranes is very effective in removing small solutes (urea and creatinine), and has been the standard for many years. With increasing insight in the devastating and clinically important effects of middle molecules (uremic toxins > 0.5 kDa), this therapeutic modality has to a large extent been replaced by high-flux HD [25-27]. However, solute diffusion coefficients decrease rapidly with increasing molecular size, even those that can fit easily through the high-flux membrane, and this fact lead to the exploration of convective therapies, such as HDF [28, 29]. Over the last five years, the use of HDF in Europe is steadily increasing, with at least 10% of the European HD population being treated with HDF in 2013 [28]. In some countries, such as Switzerland, over 60% of the dialysis patients are treated with HDF, and in northern Europe about 24% [28]. Our data confirm findings from other groups that BTP is not significantly removed during dialysis with low-flux membranes [22, 30]. Lindström *et al.* [22] studied BTP-kinetics during low-flux HD, and even an increase of 6% of the molecule was seen immediately after the dialysis session. In contrast with the findings of Gerhardt *et al.* [21], we found a clearance of the molecule by high-flux HD. The use of different dialysis membranes or differences in ultrafiltration between the studied groups could underlie this observation.

In the present study, pre-dilution HDF, using the same filter as in the high-flux HD session, resulted in a significant decrease in BTP-levels, with a 39% reduction of the baseline levels. Importantly, this decrease persisted over time, resulting in a significant decrease (-15% compared to baseline) before the next dialysis session. To the best of our knowledge, this is the first study describing the effect of HDF on BTP-levels over a whole cycle between dialysis sessions, which is important in the interpretation of BTP-levels regarding RRF estimation.

Fig. 2. Association between BTP-based eGFR and mGFR in PD patients. The difference between estimated and measured clearance is presented on the vertical (y) axis and the average of both on the horizontal (x) axis. Positive number on the y-axis represent overestimation of eGFR and negative numbers represent underestimation. Mean difference (bias) and limits of agreement are also shown.

Lindström *et al.* [22] and Gerhardt *et al.* [21] described a significant decrease of BTP-levels immediately after post-dilution HDF, but did not study later time points than 30 minutes after dialysis. The fact that in the present study, pre-dilution HDF, which is usually considered as less effective than post-dilution HDF, already resulted in clinically important changes makes it likely that post-dilution HDF would result in the same findings. Further research is warranted to gain insight in the BTP-kinetics during all routinely used dialysis techniques.

Shafi *et al.* [19] recently proposed a BTP-based formula for eGFR estimation, generated in a mixed dialysis population. They studied intra-individual variability only in nine subjects, without differentiating between HD and PD. In the present study, 172 repeated measurements were made (52 in HD and 120 in PD) and excellent reliability over time was confirmed in both groups separately. Although the number of studied PD patients is too small to make definitive statements, the level of agreement of the recently proposed formula appeared to be fair, with a tendency to underestimation of GFR compared to mGFR.

Some limitations of the present study should be acknowledged. At first, gold standard measurements of RRF are lacking, as well as data on urinary output of HD patients (Cohort 1 and 2). Next, for the HDF modality, only the predilution set-up was tested. For the variability over time of BTP levels in dialysis patients, we assume stability of renal function over three months, but parallel measurements of creatinine, urea, or urinary output are lacking. Lastly, we did not collect data on the handling of the BTP molecule by the peritoneal membrane.

Our data show that whereas BTP could be a promising surrogate marker for RRF in HD and PD, its levels should be interpreted with caution in HDF patients. The influence of HDF on BTP levels should be confirmed in larger cohorts of patients on maintenance HDF therapy. Moreover, formulas including BTP should be validated in various dialysis settings, as well as against other methods of measured GFR, before this surrogate for RRF can be implemented in clinical practice.

Disclosure Statement

Bengt Lindholm is employed by Baxter Healthcare Corporation. None of the other authors declare any conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Acknowledgements

We thank all patients who participated in the study and those who carried out the extensive clinical and laboratory work in the clinical investigational unit and the renal laboratory at division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Campus Flemingsberg, Stockholm, Sweden. The study also benefited from generous support from Amgen Inc, Karolinska Institutet Diabetes Theme Center (PS), ALF (Stockholm Council) (PS), Swedish Research council (PS), Martin Rind Foundation (PS), Njurfonden (PS), and Westmans Foundation (PS). A. Van Craenenbroeck was supported by an ERA-EDTA Short Term Fellowship. Baxter Novum is the result of a grant from Baxter Healthcare to Karolinska Institutet.

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