Thiamine Diphosphate Status and Dialysis-Related Losses in End-Stage Kidney Disease Patients Treated with Hemodialysis

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Keywords

Thiamine · Hemodialysis · Kidney · Nutrition · Supplementation

Abstract

Aim: (1) To describe the whole blood content of thiamine diphosphate (TDP), a biologically active form of vitamin B1 in end-stage kidney disease patients treated with hemodialysis (HD); (2) to establish the impact of a single HD procedure on TDP blood concentrations; and (3) to describe potential explanatory variables influencing TDP dialysis related losses, including dialysis prescription, vitamin B1 dietary intake and supplementation. **Methods:** Single-center, cross-sectional study in 50 clinically stable maintenance HD patients. The assessment of whole blood TDP with the High Performance Liquid Chromatography method, before and after a single, middle-week dialysis session and analysis of clinical and laboratory parameters potentially influencing TDP status. **Results:** We report a significant difference in TDP levels before and after HD sessions – 42.5 (95% CI 38.7–46.2) µg/L and 23.6 (95% CI 18.9–28.2) µg/L, respectively ($p = 0.000$). The magnitude of intradialytic TDP changes is highly variable among individuals and is nega-

tively associated only with the body weight of the patients ($p < 0.013$). Vitamin B1 dietary intake and supplementation do not influence whole blood TDP and dialysis-related loss of TDP. **Conclusions:** TDP, a bioactive compound of vitamin B1, is substantially lost during the HD procedure, and the magnitude of its loss is associated with the patient's body weight but it is not influenced by vitamin B1 dietary intake and standard supplementation dose.

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Introduction

Thiamine (vitamin B1) is an essential nutrient for humans. Whereas thiamine is synthesized by many plants and micro-organisms, all mammals depend on its consumption with diet. In general, body supplies of water soluble vitamins are not effectively stored in humans. This refers especially to thiamine, as the time to exhaustion of thiamine stores is the shortest when compared to all other nutrients, and it is counted in days [1]. Hence, in a condition of compromised supply, symptoms of vitamin B1 insufficiency should be expected in the first instance.

Several factors contribute to compromised thiamine status in end-stage renal disease (ESRD). Anorexia and insufficient dietary intake are regarded as the most important contributors [2, 3]. However, new contributors have emerged recently, including impaired gastrointestinal absorption by specific transporters, or the role of microbiota in the production of thiamine antagonist, oxythiamine, both, importantly, influenced by ESRD [4, 5].

Dialysis-related losses of water soluble vitamins, another important contributor to vitamin status in ESRD, are poorly understood. Recently, an important role of hemodialysis (HD) treatment in the development of vitamin C deficiency has been shown [6]. Whether the same mechanisms apply to vitamin B1 is debatable. The evidence of thiamine dialysis-related losses is scarce and contradictory [1]. The molecular weight of thiamine (266.4 Da) makes it prone to be lost by this route. The dialysis procedure is a widely accepted risk factor for the onset of Wernicke encephalopathy, and most probably this life-threatening condition is largely underdiagnosed [7–10]. Also, thiamine deficiency is regarded as one of the causative factors in dialysis-related encephalopathy [9, 11]. Therefore, the elucidation of the role of HD in maintenance of vitamin B1 status is an issue of preeminent importance. Moreover, filling the gap in knowledge about the influence of a single dialysis session on thiamine losses may help to establish what is an adequate dose of thiamine supplementation in ESRD.

In the performed study, we aimed (1) to describe the whole blood content of thiamine diphosphate (TDP), a biologically active form of vitamin B1, in ESRD patients treated with HD; (2) to establish the impact of a single HD procedure on TDP blood concentrations; and (3) to describe potential explanatory variables influencing TDP dialysis-related losses.

Patients and Methods

Patients' Characteristics

Written consent was obtained from all participants before entry into the study and the local ethics committee approved the protocol NKBBN/325/2013. We enrolled all adult participants treated with maintenance HD in our center, provided they fulfilled the inclusion criteria. The study had a cross-sectional design. The following are the exclusion criteria: HD treatment for shorter than 4 weeks, inadequate HD treatment (KT/V lower than 1.2), dysfunction of vascular access, active inflammation at the recruitment (CRP exceeding 7 mg/dL), active malignancy, acute intradialytic complications during the session (leading to the modifications of fluid removal/ultrafiltration [UF] target, administration of saline

Table 1. Demographics and clinical characteristics of the participants

Variable	Value
Age, years	57.7 (39.2–67.5)
Gender, m/f	24/26
Etiology of CKD, <i>n</i> (%)	
DN	9 (18)
HTN	8 (16)
Glomerulonephritis	17 (34)
Tubulo-interstitial	4 (8)
Polycystic kidney disease	3 (6)
CAKUT	4 (8)
Contrast induced	1 (2)
Multiple myeloma	1 (2)
Unknown	3 (6)
History of cardiovascular event, <i>n</i> (%)	11 (22)
Diabetes comorbidity, <i>n</i> (%)	15 (30)
Medication, <i>n</i> (%)	
Supplementation with vitamin B1	9 (18)
Beta-blockers	32 (64)
ACEI	11 (22)
ARB	2 (4)
Dry weight, kg	65.4 (60.2–70.6)
Dialysis vintage, months	94.7 (67.4–122.0)
Type of vascular access; fistula/ catheter, <i>n</i> (%)	38 (76)/12 (24)
Hours of dialysis per week	12.8 (12.4–13.2)
RRF, mL/24 h	349 (181–516)
Type of membrane; high flux/ low flux, <i>n</i> (%)	13 (26)/37 (74)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; DN, diabetic nephropathy; HTN, hypertensive nephropathy; RRF, residual renal function.

or glucose or shortening of HD duration), and inability to provide informed consent and reliable dietary recall. Table 1 displays the characteristics of the study group.

The majority of participants (*n* = 37) were treated with polysulfone LF (PES, Dora, Bain Medical Equipment, China) and the rest (*n* = 13) with polysulfone HF (Elisio, Nipro Corporation, Japan) dialyzer membranes. The duration of the session was 4.0–4.5 h. Blood flow was 280–300 mL/min and dialysate flow was 420–450 mL/min (according to blood flow). The UF rate during the dialysis session was calculated by the weight difference, before and after dialysis. The percentage reduction in the vitamin values after dialysis was calculated using the following formula:

$$[(\text{value before HD} - \text{value after HD}) / \text{value before HD}] \times 100.$$

Non-fasting blood samples were collected in tubes with ethylenediamine tetraacetic acid or no additive, before the HD session from the arterial shunt needle. At the end of the dialysis session, dialysate flow was stopped after 5 min. The arterial line was discon-

nected and sample was taken within 5–10 s. Plasma was separated after centrifugation and analyzed immediately. Lysates of blood with ethylene-diamine tetraacetic acid were stored at –80°C for use in further analyses.

We measured whole blood TDP and blood urea nitrogen (BUN) before and after HD, as well as plasma creatinine, albumin, sodium (Na) and blood morphology indices (hemoglobin, hematocrit and the number of leucocytes white blood cell [WBC]) before the HD procedure.

Vitamin B1 intake in the day preceding the sampling was calculated on the basis of a 24-h diet recall. Six patients had difficulty in providing accurate recall and were thus excluded from data processing. Participants listed all foods and beverages consumed during the preceding 24 h. The quantification of consumed amounts included units, portions, and household measures. To ensure the accuracy of the recall, each record was evaluated by a skilled dietitian and patients were asked to provide additional information, if indicated. Data from the recall were processed with the use of software Dietetyk (JuMaR, 2012) based on the local food composition tables [12] and corrected for losses during food processing. The dose of vitamin B1 supplement was 1.1 mg as recommended [13]. The dose of supplement was added to the daily intake. The adherence to the supplementation was low (18%) due to the lack of reimbursement of this procedure in our country.

We analyzed demographic and clinical data (age, gender, body weight, time on dialysis, albumin concentration, diabetes mellitus (DM) and cardio-vascular comorbidity, residual renal function (RRF), session duration time, UF rate, type of the dialyzer membrane, KT/V, medication and dietary vitamin B1 intake, as predicted contributors that may influence thiamine status.

Laboratory Measurements

All laboratory measurements, with the exception of TDP, were performed with an autoanalyzer (Modular Roche), using standard methods as follows: BUN with the use of spectrophotometric method, creatinine with colorimetric kinetic test, and protein with colorimetric method. Complete blood count was performed with flow cytometry (Sysmex XE 2100D Hematology Analyser).

Whole blood TDP was investigated employing Reversed Phase High Performance Liquid Chromatography (HPLC) with fluorescence detection. HPLC system (Waters, USA) was equipped with a W-600 2-channel pump and controller with a degassing unit, W2707 autosampler, and W474 fluorescence detector. Waters Empower 2 software was applied to collect and process the chromatographic runs. Commercially available reagent kit, designed for assaying of vitamin B1 in whole blood samples (cat. No. 35000, Chromsystems GmbH, Munich Germany), was employed for monitoring TDP levels in whole blood. Chromatographic analyses were performed at room temperature, applying the isocratic mode with the flow rate of 1.0 mL/min, and the fluorescence detector operating at moderate sensitivity (gain = 100 mV), set at excitation/emission wavelengths of 367 nm/435 nm respectively. The injection volume was set at 50 µL for each run. Analyses were taken in triplicate for each sample and the retention times of the monitored analyte (TDP) fell in the range of 3.0–3.5 min. The following equation was used to calculate the concentration (in µg/L) of TDP in patients' whole blood samples:

$$C_{TDP, sample} = \frac{A_{sample}}{A_{calibrator}} \times C_{TDP, calibrator}$$

Table 2. Hemodialysis prescription, laboratory results before the session, and the thiamine intake in the preceding day

Variable	Value, mean (95% CI)
TDP, µg/L	42.5 (34.9–52.9)
BUN, mg/dL	61.3 (56.5–66.2)
Creatinine, mg/dL	8.6 (7.9–9.4)
Albumin, g/L	33.7 (32.8–34.6)
Na, mmol/L	138.1 (137.2–139.1)
Hemoglobin, g/L	11.0 (10.7–11.3)
RBC, 10 ⁶ /µL	3.5 (3.41–36.2)
WBC, 10 ³ /µL	6.7 (6.18–7.30)
UF, mL	2,474 (2,100–2,847)
UF rate, mL/h	574 (495–653)
Kt/V _{urea}	1.67 (1.60–1.74)
Dietary intake of vitamin B1, mg	0.96 (0.80–1.12)

TDP, thiamin diphosphate; BUN, blood urea nitrogen; RBC, red blood cells; WBC, white blood cells; UF, ultrafiltration.

where: $C_{TDP, sample}$ – is the concentration (in µg/L) of TDP in the derivatised sample; A_{sample} – is the relative area under the chromatographic signal for the derivatised sample; $A_{calibrator}$ – is the relative area under the chromatographic signal for the derivatised calibrator; $C_{TDP, calibrator}$ – is the concentration (in µg/L) of TDP in the derivatised calibrator. The reference range of vitamin B1 (TDP) in healthy individuals performed with the reagent kit falls in the range 28–85 µg/L.

Statistics

Distributions of all data were tested according to the Shapiro-Wilk and Kolmogorov-Lilliefors tests. Numerical variables are expressed as mean (95% CI); categorical data are expressed as numbers and percentages, as appropriate. TDP and BUN values before and after HD were compared with non-parametric variables. Statistical significance was set at the level of $p < 0.05$. The associations between the dialysis-related change of TDP and other parameters were investigated by multiple linear regression analysis in a model including TDP change (in %) versus intradialytic change of BUN, weight, UF rate, type of dialyzer membrane, Kt/V, RRF, HD duration time, thiamine intake, gender, and a diagnosis of DM.

Results

Table 2 summarizes parameters of a dialysis prescription and laboratory results before the dialysis session. Individual values of TDP concentration before and after the dialysis procedure are displayed in Figure 1. All but one individual measurement of blood TDP concentration before dialysis were within the reference range of healthy individuals, according to the method employed for TDP determination. TDP before HD was not associated with any analyzed clinical or laboratory parameter including weight,

Table 3. Univariate analysis of relation between the TDP dialysis-related changes and selected clinical parameters

Variable	Coefficient of regression	<i>p</i> value
Intradialytic change of BUN, %	0.057	0.716
Weight, kg	−0.440	0.003
UF volume, mL	−0.060	0.673
UF rate, mL/h	−0.054	0.710
Kt/V	0.085	0.555
RRF, mL/24 h	−0.208	0.147
HD session duration time, h	−0.123	0.393
Diet thiamine intake, mg/24 h	0.003	0.987

TDP, thiamine diphosphate; BUN, blood urea nitrogen; UF, ultrafiltration; RRF, residual renal function.

Fig. 1. Individual ($n = 50$) thiamine diphosphate (TDP) concentrations before and after hemodialysis sessions.

UF, type of membrane, Kt/V, RRF, HD duration time, thiamine intake, gender, diagnosis of DM, RBC, WBC, BUN, albumin, Na, or creatinine. TDP before HD was also independent from the content of vitamin B1 in diet in the preceding day and the supplementation with vitamin B1.

After dialysis, the concentration of TDP in whole blood decreased in all cases. Mean measured TDP whole blood concentrations before and after HD session were 42.5 (95% CI 38.7–46.2) µg/L and 23.6 (95% CI 18.9–28.2) µg/L respectively ($p = 0.000$). The mean reduction of TDP concentration after HD was 43.9% (95% CI 34.9–52.9), characterized by a very high variability coefficient of 71.5%. Mean measured plasma BUN concentrations be-

fore and after HD were 61.3 (95% CI 56.5–66.2) mg/dL and 16.0 (95% CI 14.3–17.6) respectively ($p = 0.000$). The mean reduction of plasma BUN after HD was 73.7% (95% CI 71.3–76.0), with a variability coefficient of 11.4%. TDP after HD was not associated with any analyzed clinical or laboratory parameter including weight, UF, type of membrane, Kt/V, RRF, HD duration time, thiamine intake, the supplementation with vitamin B1, gender, diagnosis of DM, RBC, WBC, BUN, albumin, Na or creatinine.

In both univariate and multivariate regression analyses of clinical and laboratory parameters, only weight was identified as a determinant of TDP loss during single HD sessions (Tables 3, 4). The association was negative ($\beta = -0.898$; $p < 0.013$). Values of all parameters included into the multivariate model are summarized in Table 4. The plot of TDP concentration change before and after HD versus patients' body weight is depicted in Figure 2.

Discussion

To date, only a few studies assessed thiamine status in dialysis patients, and only 4 have reported measurements of thiamine status before and after single HD sessions [14–17]. However, those studies yielded conflicting results, claiming decrease [16], no change [17], or even increase of thiamine after the HD procedure [14, 15]. Differences in those findings reflect (most probably) the diversity of the methodological approach. Nevertheless, the evidence existing to date does not provide an unambiguous knowledge about a factual influence of the HD process on thiamine status.

The thiamine content is distributed unequally in compartments of whole blood with the majority of thiamine (75%) found in erythrocytes and only 10% in plasma [18]. Yet, most studies evaluating vitamin status rely on its plasma levels, which do not necessarily reflect adequate vitamin content in tissues. Further, the principal and biologically active form of thiamine is the diphosphate, and this form acts as a cofactor for numerous enzymatic activities. TDP constitutes the prevalent form of thiamine and its concentrations are depleted from erythrocytes at a rate similar to depletion from other tissues [19]. Thus, the determination of TDP in whole blood seems to be the best indicator of rapid changes of thiamine content during the HD procedure and that is why we choose it to elucidate the previous equivocal findings.

Consistent to the findings of previous reports, we have not identified significant thiamine deficiency in pre-dialysis measurements as compared to reference values for

Table 4. Results of multivariate regression analysis of variables potentially influencing the TDP dialysis-related change

Explanatory variable	Regression coefficient <i>b</i>	SE	<i>t</i> value	<i>p</i> value
Constant	12.885	67.899	0.190	0.850
Intradialytic change of BUN, %	0.045	0.622	0.070	0.468
Weight, kg	-0.898	0.345	-2.605	0.013
UF volume, mL	0.004	0.004	0.865	0.392
Type of membrane (high flux vs. low flux)	1.498	11.381	0.132	0.896
Kt/V	-20.546	23.898	-0.860	0.395
RRF, mL/24 h	-0.006	0.008	-0.741	0.463
HD session duration time, h	6.654	4.335	1.535	0.133
Diet thiamine intake, mg/24 h	-11.101	11.615	-0.956	0.345
Gender (M vs. F)	17.830	11.506	1.550	0.129
Diabetes mellitus	7.579	10.349	0.732	0.468

TDP, thiamine diphosphate; BUN, blood urea nitrogen; UF, ultrafiltration; RRF, residual renal function; SE, standard error assessed for *b*; *t*, actual *t*-test parameter; *p*, actual significance level.

Fig. 2. Concentration of thiamine diphosphate (TDP) changes before and after hemodialysis sessions plotted against patients' body weight.

healthy humans [14, 15, 17, 20, 21]. However, in view of high concentrations of oxythiamine, an antythiamine compound, reported recently in ESRD by Zhang et al. [5], the reference concentrations of thiamine might not necessarily comply with its increased needs in hemodialysed patients. The astonishing lack of association between TDP levels and vitamin B1 intake reported in dietary recalls or between the presence or lack of vitamin B1 supplementation reflects either the prominent role of thiamine produced by gut microbiota in thiamine homeostasis or the impaired process of thiamine phosphorylation into TDP in ESRD. These

findings point to the need for revising our understanding of derangements in the metabolism of micronutrients in ESRD. It seems that mechanisms beyond the dietary intake or standard supplementation may play an important role in maintaining the vitamin status in ESRD.

We observed significant decreases of TDP levels after dialysis sessions. This observation is in accordance with the previous findings of Heinz et al. [16], although the decrease was much higher in our study. This could be explained by the fact that the total thiamine, not TDP, was determined in the above-mentioned work. When the total thiamine content is measured, those forms of thiamine, which increase after HD may compensate for TDP loss. This may also explain the cause of a few previous findings of thiamine increase after dialysis session [14, 15]. The molecular weight of free thiamine (266.4 Da) is lower than that of its phosphorylated derivative TDP (425.3 Da). However, in all patients, TDP decreased after dialysis sessions, which support the hypothesis of its loss through the dialysis membrane.

Most potential determinants of dialysis thiamine losses such as UF, type of membrane, KT/V, RRF, thiamine intake, and so on did not associate with TDP levels. For example, we found no association between the type of the membrane (high flux vs. low flux) and the percentage of thiamine change, which goes in line with the findings of Heinz et al. [16]. Also, dialysis adequacy, UF, or duration of the HD session did not associate with TDP loss. Although both BUN and TDP decreased several-fold during HD, the pattern of their loss seemed not related. Especially, the percentage of loss of BUN was comparable between

patients, while the loss of TDP displayed a high variability. Interestingly, the only impact on this variability was revealed through the weight of the patient. It means that higher intradialytic loss of vitamin B1 was observed in patients with a lower body weight. We are not aware of any reports analyzing the metabolism of thiamine in humans of different weights. However, taking into account that the largest pool of thiamine is stored in muscles, the difference of muscle mass could plausibly explain our observation. This finding of the negative association between percentage of TDP loss and body weight suggests that patients are able to compensate for dialytic changes of TDP by releasing vitamin B1 from muscle stores.

Our study provides several hints on how to decide on vitamin B1 supplementation in HD patients. First of all, the whole blood concentration of an active compound of vitamin B1 (TDP) is not importantly different, in this group, from that expected in the general population. This does not necessarily mean that such a concentration is adequate in HD patients but may suggest that decreased vitamin B1 losses with urine compensate for dialytic losses that we have shown. Second, the current supplementation dose (1.1 mg a day) seems not to affect TDP blood concentrations and dialytic losses. This may raise the question of the ability to absorb the supplement dose within this range in a condition of ESRD that is associated with gastrointestinal tract impairment. Third, patients who may benefit most from intensifying the supplementation are those with low muscle mass unable to maintain their vitamin body stores.

Our study has several limitations. First, the number of patients was relatively small. This was a consequence of the single-center design of the study. Second, we did not analyze changes of thiamine concentration in dialysate, which was caused by the fact that TDP concentration in dialysate sample would be undetectable, while the collection of whole dialysate (ca. 100 L) was logistically impos-

sible. Hence, it cannot be ruled out that TDP was not only lost to dialysate but also changed its form to another metabolite of thiamine, for example, thiamine monophosphate, during the dialysis procedure.

On the other hand, we regard the analysis of whole blood concentration of TDP (reflecting tissue content of vitamin B1) as a particular strength of the study. Most data published so far analyzed serum values, or transketolase activity, which make unreliable reflections of vitamin B1 status in ESRD [5].

In summary, we report that TDP, a bioactive compound of vitamin B1, substantially decreases during the HD procedure. The quantity of this decrease is not associated with dialysis prescription or thiamine intake, and the only clinical parameter associated with its magnitude is the patient's weight. In view of the role played by thiamine in pathophysiology, our observation may offer an argument in favor of intensifying the supplementation with vitamin B1 as the standard recommended dose of 1.1 mg daily did not influence the status of an active thiamine form. In view of our findings, the individuals who may benefit from supplementation the most are those with low muscle mass (women, patients of an advanced age, undernourished).

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Disclosure Statement

All authors declare that they have no conflicts of interest to disclose.

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