Nutrition estimation of dialysis patients by on-line monitoring and kinetic modelling

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Abstract. The aim of this study was to estimate a nutritional parameter, normalized protein nitrogen appearance (nPNA), for haemodialysis (HD) patients by on-line monitoring with the optical dialysis adequacy monitor (DIAMON) prototype, by the modified direct dialysis quantification (mDDQ), and by the volume-variable single-pool urea kinetic modelling (VVSP UKM). Ten HD patients were monitored on-line by the DIAMON prototype during three consecutive haemodialysis sessions during one week. Blood samples were taken and the total dialysate collection (TDC) was performed during all dialyses. The nPNA values were estimated by DIAMON, mDDQ and VVSP UKM; nPNA was normalized by $V/0.58$ and by the measured dry body weight, efBW. Individual nPNA for each patient during a seven-day period was estimated using UV-absorbance measured on-line by the DIAMON prototype. The nPNA values (mean $\pm$SD) in g/kg/day for the total material were: 1) 0.74 ± 0.12 from DIAMON ($N = 28$), 0.90 ± 0.26 from mDDQ ($N = 29$) and 0.90 ± 0.23 from VVSP UKM ($N = 30$) normalized by $V/0.58$, and 2) 0.68 ± 0.10 from DIAMON ($N = 28$), 0.72 ± 0.19 from mDDQ ($N = 29$) and 0.80 ± 0.18 from VVSP UKM ($N = 30$) normalized by efBW. The optical device for monitoring the dialysis adequacy enables individual nPNA estimation for each patient using continuous, on-line UV-absorbance measurements. The results are comparable to the nPNA values obtained by the kinetic modelling. Still a question remains concerning the normalization of PNA.

Key words: dialysis, nutrition, urea, protein nitrogen appearance, ultraviolet absorption, on-line monitoring, kinetic modelling.

1. INTRODUCTION

Dialysis is the most common method for treating advanced and permanent kidney failure. The most popular clinical parameters from urea kinetic modelling (UKM), characterizing dialysis adequacy, are the dialysis dose Kt/V and the

normalized protein nitrogen appearance nPNA. The dialysis dose has been reported to have a great significance for the outcome of the dialysis treatment [1,2]. The nPNA is one tool to assess malnutrition, which is a strong predictor of death among haemodialysis patients [2]. Formal UKM, based on the blood samples, calculates the urea distribution volume (V) and the urea generation rate (G) by mathematical iteration [3]. The VVSP UKM model is suggested for dialysis adequacy estimation [1,2].

The total dialysate collection technique, or direct dialysis quantification (DDQ), uses the total removed urea nitrogen (TRU) through collecting the entire dialysate, exiting the dialyser over a dialysis treatment [4]. The mDDQ, using TRU and the blood samples, is successfully applied for validation of dialysis adequacy [5], enabling similarly to UKM iteratively calculate the G and V values. An alternative approach is to estimate TRU over a 7-day period, which corresponds to the urea generated within the same time period for the anuric patients, and calculate nPNA without blood sampling [4]. An approximation of the mentioned method is nPNA determination from a single measurement of dialysate urea, assuming that the first, midweek, and last dialysis account for nearly constant fractions of the week's urea removal for thrice weekly dialysis cycle [6].

On-line monitoring of the dialysis dose has been suggested as a valuable tool to ensure adequate dialysis prescription [7]. Recently spectrophotometrical sensors for on-line monitoring of total ultraviolet (UV) absorbance or urea in the spent dialysate have been presented, aiming to follow continuously a single haemodialysis session [8–11]. A good correlation between UV-absorbance and a small removed waste solute such as urea enables the determination of Kt/V for urea [12], and nPNA [13]. Furthermore, a new prototype device, DIAMON, has been designed for continuous on-line estimation of delivered dialysis dose from optical dialysate measurements [14].

Because protein requirements are determined primarily by fat-free, oedema-free body mass, PNA is usually normalized to some function of body weight (e.g., actual, adjusted, or standardized [NHANES II] body weight) [1]. A way to normalize nPNA is to use the "kinetic body weight" $V/0.58$, where V is calculated using some iterative algorithm or anthropometric formula [15]. The most common anthropometric formula is called the Watson formula [1]. The measured dry body weight or oedema free body weight (efBW) [2], obtained post-dialysis in HD patients, has been used [6], which may lead to nPNA underestimation [15,16]. However, efBW may be used effectively when the value is close to the standardized body weight [1].

The aim of this study is to estimate patient nutritional parameter nPNA individually by the on-line DIAMON prototype, by formal urea kinetic modelling, and by modified direct dialysis quantification.

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2. SUBJECTS AND METHODS

2.1. Subjects

This study was performed after approval of the protocol by the Tallinn Medical Research Ethics Committee at the National Institute for Health Development, Estonia. A consent was obtained from all participating patients.

Ten patients were investigated, three females and seven males, mean age 62.6 ± 18.6 years, on chronic thrice-weekly haemodialysis treatment. Each patient was monitored during three consecutive dialysis sessions during one week. As dialysis access four patients had arterio-venous fistula, three patients had artificial graft, and three patients had temporary catheter of *v. jugularis* or *femoralis*. All patients were dialysed using a two-needle system. All patients were dialysed with polysulfone membrane dialysers (Fresenius Medical Care, Germany): (1) four patients with 12 treatments by low flux dialyser F8 HPS with an effective membrane area of $1.8\,\mathrm{m}^2$ and an ultrafiltration coefficient of 18 mL/h·mmHg; (2) one patient with three treatments was dialysed with low flux membrane dialyser F10 HPS with membrane area $2.2\,\mathrm{m}^2$, ultrafiltration coefficient of 21 mL/h·mmHg; (3) five patients on 15 sessions with high flux dialyser FX 80 with effective membrane area of $1.8\,\mathrm{m}^2$ and ultrafiltration coefficient of 59 mL/h·mmHg. The dialysate flow rate was fixed at 500 mL/min. The prescribed blood flow was 350 or 300 mL/min during the two treatments within the week according to the patient records and 245 mL/min for one treatment, and was kept constant throughout the dialysis session. The durations of dialysis sessions were from 190 to 240 min. The dialysis machine used in the study was Fresenius 4008H (Fresenius Medical Care, Germany).

2.2. Sampling and laboratory analysis

Blood samples were drawn before the start of the dialysis treatment, at the end of dialysis, and 30 min after dialysis, using the slow flow sampling technique. Total dialysate collection (TDC) started when the blood filled the dialyser and ended when the blood was returned to the patient at the end of the dialysis. All spent dialysate was collected in a tank, calibrated against a weighting-machine. After careful stirring and recording of the weight of the collected spent dialysate, the TDC sample (U_{TDC}) was collected. The concentration of urea was measured at the Clinical Chemistry Laboratory at North-Estonia Medical Centre using a standardized method. The accuracy of the method for determination of urea in blood and dialysate was $\pm5\%$.

2.3. Normalized protein nitrogen appearance

The value of nPNA in g/kg/day, A_{nPNA}, was estimated as

$$A_{\mathrm{nPNA}} = 9.35 \frac{G}{V/0.58} + 0.17. \tag{1}$$

Obligatory loss of dietary protein in stool and via skin shedding represent the constant term 0.17 (g protein/kg body weight/day). The G and V values were obtained from the iterative mDDQ and VVSP UKM calculations. Patients' residual clearance was considered to be negligible and was not taken account.

2.4. Modified direct dialysate quantification

The parameters V and G were calculated according to the mDDQ method solving iteratively two equations [5]:

$$V = \frac{U_{\mathrm{TRU}} - G(T+0.5) - F_{\mathrm{UF}}\dfrac{C_{\mathrm{pre}}}{0.93}}{(C_{\mathrm{pre}} - C_{\mathrm{r}})/0.93}, \tag{2}$$

$$G = \frac{V\left(\dfrac{C_{\mathrm{pre}} - C_{\mathrm{r}}}{0.93}\right) + \left(W\dfrac{C_{\mathrm{pre}}}{0.93}\right)}{\theta - 30}, \tag{3}$$

where U_{TRU} is the amount of TRU, C_{pre} and C_{r} are the blood concentration of urea at the start of dialysis and the rebound urea concentration in mmol/L, F_{UF} is the value of the total ultra filtration UF, W is the total interdialytic weight gain in kg, T and θ are the dialysis session length and the interdialytic time interval in min, respectively.

2.5. Variable-volume single-pool urea kinetic modelling

The variable-volume single-pool urea kinetic modelling was used to calculate V and G values from the following equations:

$$V = F_{\mathrm{UF}}\left\{\left[1 - \left(\frac{G - C_{\mathrm{post1}}(K + K_{\mathrm{r}} - F_{\mathrm{UF}}/t)}{G - C_{\mathrm{pre1}}(K + K_{\mathrm{r}} - F_{\mathrm{UF}}/t)}\right)^{\frac{F_{\mathrm{UF}}/t}{K + K_{\mathrm{r}} - \mathrm{UF}/t}}\right]^{-1} - 1\right\}, \tag{4}$$

$$G = \frac{(K_{\mathrm{r}} + W/\theta)\left\{C_{\mathrm{pre2}} - C_{\mathrm{post1}}[(V+W)/V]^{\frac{K_{\mathrm{r}} + W/\theta}{W/\theta}}\right\}}{1 - [(V+W)/V]^{\frac{K_{\mathrm{r}} + W/\theta}{W/\theta}}}, \tag{5}$$

where C_{pre1} and C_{post1} are the blood concentrations of urea at the start and at the end of the first dialysis in mmol/L, C_{pre2} is the blood concentration of urea at the start of the second dialysis in mmol/L, K and K_{r} are the dialysers blood urea clearance and patients' renal residual clearance in mL/min, respectively.

The dialysers blood urea clearance in vitro, K_b, was calculated as

$$K_b = Q_b Q_d \frac{1 - e^{\left(-K_0 A \frac{Q_d - Q_b}{Q_d Q_b}\right)}}{Q_d - Q_b e^{\left(-K_0 A \frac{Q_d - Q_b}{Q_d Q_b}\right)}},\tag{6}$$

where $K_0 A$ is the dialyser mass transfer area coefficient in mL/min, and Q_b is the blood flow rate in mL/min. Effective blood urea clearance in vivo, K, was estimated as being 20% lower than the K_b value [17].

2.6. Dialysis adequacy monitor prototype

The DIAMON prototype (AS Ldiamon, Estonia) was connected to the fluid outlet of the dialysis machine with all spent dialysate passing through an optical cuvette during on-line experiments (Fig. 1). The optical cuvette was a quartz tube, permeable for the UV-radiation, with a diameter of 10 mm. The transmitted light (280 ± 5 nm) intensity of the spent dialysate was measured. The used wavelength was shown to be both technically and methodologically suitable for dialysis dose estimation having a good correlation with the dialysis quality marker solute urea [18]. The sampling frequency was set to 20 samples/min. The obtained intensity values were processed to obtain UV-absorbance, presented on the computer screen by using Ldiamon's software (AS Ldiamon, Estonia, for Windows). The UV-absorbance A was calculated as

$$A = \log \frac{I_r}{I_{r+s}},\tag{7}$$

where I_r is the intensity of transmitted light through the reference solution (pure dialysate) and I_{r+s} is the summated intensity of transmitted light through the reference solution containing the solutions under study (pure dialysate + waste products from the blood).
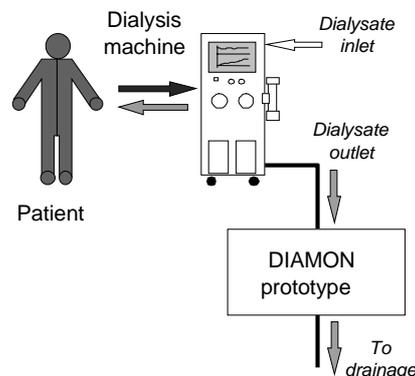
Fig. 1. The clinical experimental set-up.

The calculation of A_{nPNA} for the DIAMON prototype was based on the earlier exploited methodology [6], according to the first, midweek, and last dialyses account for nearly constant fractions (37.9, 32.1, and 30.0%, respectively) of the week's urea removal. This leads to an equation, where the amount of urea is approximated from measuring totally removed urea (TRU) from only one of the three treatments and A_{nPNA} can be calculated as

$$A_{nPNA} = F_i\left(\frac{U_{TRU,i}}{V/0.58}\right) + 0.17, \qquad (8)$$

where $U_{TRU,i}$ and F_i are the amount of urea nitrogen in mg dialysed from the patient, and the fractional factor for the first ($i=1$), midweek ($i=2$) or last dialysis in week ($i=3$), respectively; $F_1 = 2.45$, $F_2 = 2.89$, $F_3 = 3.10$. The value of V was obtained from the Watson formula.

TRU was estimated by the DIAMON prototype using the on-line UV-absorbance measurements according to the total dialysate collection method under assumptions that the dialysate flow Q_d in L/min is constant, the total ultra filtration F_{UF} in kg is known and 1 kg = 1 L of the dialysate, as

$$U_{TRU} = U_{TDC}(Q_d T + F_{UF}) = (SA_{mean} + I)(Q_d T + F_{UF}), \text{mmol}, \qquad (9)$$

where U_{TDC} in mmol/L is the urea concentration of the collected spent dialysate during the particular haemodialysis session and A_{mean} is the mean of all UV-absorbance values from the start to the end of the dialysis. The dialysate urea values from the last treatment of the week and the corresponding on-line UV-absorbance values were used for a regression line between the UV-absorbance and dialysate urea, from which the parameters slope S and intercept I were obtained. The value of G (mg/min) was estimated using totally removed urea and interdialytic time interval θ, assuming that the urea generated is equal to the amount of urea removed.

2.7. Statistical analysis

The results are presented as mean $\pm$SD. Student's t-test (two-tailed) was used to compare means for different methods and $p = 0.05$ was considered significant.

3. RESULTS

The individual nPNA for each patient for three consecutive dialysis treatments during a seven-day period from UV-absorbance, measured on-line by the DIAMON prototype, is presented in Fig. 2. The results for two sessions are missing due to the technical failure in computer during the data collection. Similar nPNA behaviour was obtained also for mDDQ and VVSP UKM.
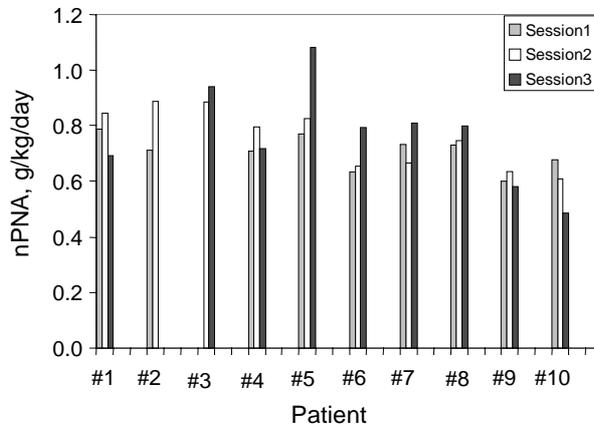
Fig. 2. Individual nPNA in g/kg/day for each patient during a seven-day period from UV-absorbance, measured on-line by the DIAMON prototype.

Figure 3 shows the estimated G values (mean ±SD) in mg/min for the total material from the UV-absorbance measured by the DIAMON prototype, from mDDQ and from VVSP UKM using blood and dialysate urea samples. The mean ±SD values of G in mg/min were: 4.50 ± 1.27 from DIAMON (number of HD sessions $N = 28$), 4.45 ± 1.75 from mDDQ ($N = 29$) and 5.17 ± 1.77 from VVSP UKM ($N = 30$). The mean G values for DIAMON, mDDQ and VVSP UKM were not statistically different ($p < 0.05$).

The estimated mean BW value (mean ±SD) in kg for the total material (Fig. 4), calculated as $V/0.58$, was by the Watson formula 74.84 ± 16.33 ($N = 30$), by mDDQ 58.04 ± 14.31 ($N = 29$), and by VVSP UKM 67.58 ± 13.31 ($N = 30$). Additionally, the measured efBW for the studied patients was
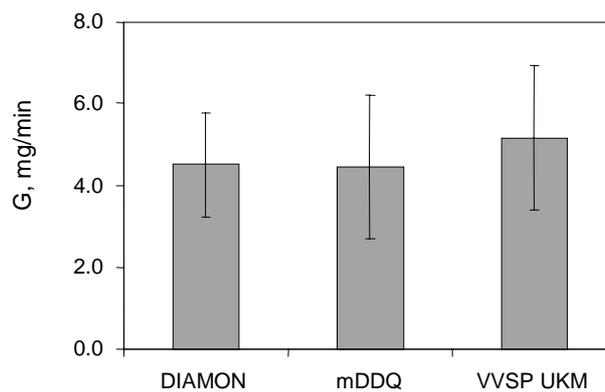
Fig. 3. Estimated urea generation rate G values (mean ±SD) for the total material from the UV-absorbance, measured by the DIAMON prototype (number of HD sessions $N = 28$), from mDDQ ($N = 29$) and VVSP UKM ($N = 30$) calculations using blood and dialysate urea samples.

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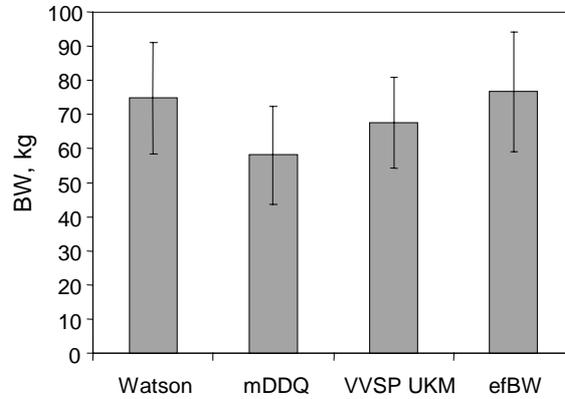
Fig. 4. Estimated BW values (mean ±SD) for the total material calculated by the Watson formula ($N = 30$), by mDDQ ($N = 29$) and by VVSP UKM ($N = 30$) as $V/0.58$, and the dry body weight, efBW ($N = 30$).

76.60 ± 17.56 kg ($N = 30$), and is presented for comparison. efBW was statistically different compared to the kinetic body weights ($p < 0.05$), and the anthropometric BW was different compared to the BW value by mDDQ ($p < 0.05$).

Figure 5 depicts the nPNA values (mean ±SD) for the total material from the UV-absorbance, measured by the DIAMON prototype, from mDDQ, and from VVSP UKM calculations, normalized by $V/0.58$ and by the dry body weight, efBW. The mean ±SD values of nPNA (g/kg/day) were: (1) 0.74 ± 0.12 from DIAMON ($N = 28$), 0.90 ± 0.26 from mDDQ ($N = 29$), and 0.90 ± 0.23 from VVSP UKM ($N = 30$), normalized by $V/0.58$; (2) 0.68 ± 0.10 from DIAMON ($N = 28$), 0.72 ± 0.19 from mDDQ ($N = 29$), and 0.80 ± 0.18 from VVSP UKM ($N = 30$) normalized by efBW. The mean nPNA values from mDDQ and from
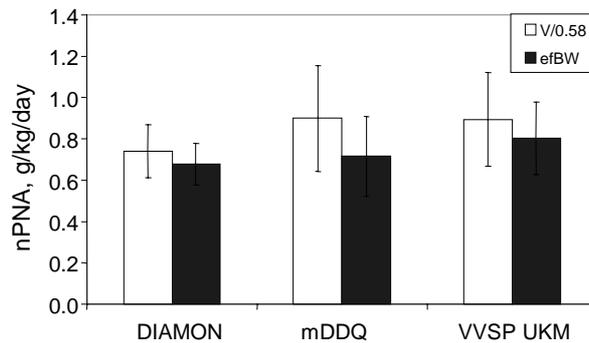
Fig. 5. Estimated nPNA values (mean ±SD) in g/kg/day for the total material from the UV-absorbance, measured by the DIAMON prototype ($N = 28$), from mDDQ ($N = 29$) and from VVSP UKM ($N = 30$) calculations, normalized by $V/0.58$ and by the dry body weight, efBW.

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VVSP UKM, normalized by the kinetic body weights, were higher compared to nPNA values from DIAMON, normalized by the anthropometric BW ($p < 0.05$). Also a higher nPNA value was obtained by UKM VVSP compared to nPNA values from DIAMON, normalized by efBW ($p < 0.05$).

4. DISCUSSION

The optical dialysis adequacy sensor, DIAMON, would facilitate HD dialysis adequacy monitoring, providing continuous, on-line measurements of dialysis dose and individual follow-up of dietary protein intake of HD patients.

The individual nPNA monitoring of each patient during a seven-day period by the DIAMON prototype shows how nPNA can vary depending on the treatment day and the patient (Fig. 2). The lower outcome for two patients relative to others, who had several dialysis related difficulties (#9 was a new dialysis patient with hypoalbuminemia, and #10 noncompliant with the treatment), is clearly seen from the nPNA recordings. Considering that the urea generation rate G is not constant over the interdialytic period [19] and day-to-day variations in daily protein intake may result in significantly fluctuating nPNA; nPNA, calculated as an average of nPNA values over a seven-day period for each patient, could be a reasonable alternative for decision making instead of nPNA from individual sessions.

The estimated mean G values for the total material were relatively close for different methods (Fig. 3). The mean values from DIAMON and mDDQ were slightly lower compared to VVSP UKM being still not statistically different. This can be due to the methodological factors described in relation to nPNA below. The level of mean G values was comparable to the reported values by earlier studies [20].

The estimated mean BW values for the total material, calculated by the kinetic or anthropometric formula, show that the results depend on the methodology (Fig. 4). For comparison, the measured dry body weight efBW is shown. The BW from mDDQ was lower than BW from the anthropometric and VVSP UKM methods, or measured as efBW. Lower V from DDQ than from UKM is observed also by other authors [21].

The malnutrition of patients that can be suspected from these results was still not evident because the mean albumin level was 38.6 g/L. The anthropometric formula by Chertow et al is suggested by guidelines, claiming that the Watson formula underestimates V about 7.5% [1]. This will cause the estimated BW to approach more to efBW and deviate from iteratively calculated values. At the same time, calculation of BW using Chertow's method requires information about the patient's age, sex and diabetic status in addition to measurements of the height and weight. Adjusted oedema-free body weight (aBWef), based on the dry body weight and the standard body weight, has been recommended for nPNA normalization [2]. However, aBWef includes NHANES II (National Health and Nutrition Examination Survey) tables specific to US and may not be suitable for

other countries [15]. With extreme obese or oedematous patients, care must be taken to estimate V and PNA [22] that could be valid for some studied patients but not in general. One solution could be to use the lean body mass to normalize PNA [16].

Figure 5 indicates higher nPNA with mDDQ and VVSP UKM compared to TRU-based equation, used by DIAMON when normalized by the anthropometric and the kinetic body weights. Higher nPNA with VVSP UKM, compared to urea output measurements, is reported also in [16]. Two sources of errors that must be considered when estimating nPNA from UKM are the rebound effect and neglected residual function [22]. The preliminary check revealed that the mean nPNA value from VVSP UKM (about 7% lower when rebound), taken 30 min after dialysis, was used instead of direct postdialysis blood urea. The residual function was not taken into account in this study. However, considering the residual function, a higher nPNA value should be obtained for all methods. Moreover, correct estimation of *in vivo* dialysers blood urea clearance is important in VVSP UKM [4].

Interestingly, the lower mDDQ G value (Fig. 3) is compensated by the lower mDDQ V value (Fig. 4) leading to equal mean nPNA compared to nPNA from VVSP UKM. This is not the case when normalized by efBW (Fig. 5). Considering that DIAMON included only dialysate-based TRU, VVSP UKM solely the blood samples, and mDDQ both plus the rebound effect, certainly some differences will appear. The mDDQ gives higher nPNA compared to DIAMON (using solely TRU-based formulae and normalized by the anthropometric BW) because of the lowest "kinetic body weight" from mDDQ. Similarly, VVSP UKM has the "kinetic body weight" lower than the anthropometric BW but a higher G value, leading to higher nPNA than the TRU-based formulae, applied for the DIAMON prototype. These methodological differences should be explored further.

The overall mean nPNA for the studied patients is lower compared to the recommended value 1 g/kg/day. The reason could lie in the design of the study, since lower blood flow than usually prescribed was applied during one dialysis for all patients. Additionally, two patients (#9 and #10) had several dialysis-related difficulties. Moreover, the patient #4 received thrice-weekly haemodialysis treatment instead of the prescribed four times per week dialysis. These factors together influence the nPNA level, indicating the importance of continuous dialysis adequacy monitoring.

In practice, the clinical judgment and longitudinal assessment of body weight and other nutritional measures should be used to assess the response to dietary therapy and to make further decisions concerning dietary management [1].

5. CONCLUSIONS

The optical dialysis adequacy monitoring device enables individual nPNA estimation for each patient using continuous on-line UV-absorbance measure-

ments. The results are comparable to the nPNA values obtained by the kinetic modelling. Still a question remains concerning the normalization of PNA.

ACKNOWLEDGEMENTS

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Dialüüsipatsientide toitumuse hindamine *online*-monitooringu ja kineetilise modelleerimise abil

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Optiline dialüüsi adekvaatsuse monitooring reaalajas pakub võimaluse hinnata dialüüsi doosi ja toitumuse parameetrit vereproove võtmata. Artiklis on käsitletud toitumuse parameetrit nPNA, mida on hinnatud optilise dialüüsi adekvaatsuse monitoriga DIAMON ja kahe dialüüsi kvaliteeti hindava kineetilise mudeliga – mDDQ ning VVSP UKM-iga. Tulemuste põhjal on järeldatud, et DIAMON võimaldab nPNA väärtust individuaalselt jälgida. Tulevikus on vajalik uurida nPNA normaliseerimisega seotud probleeme.