Original Article

Association of Dietary Protein Intake and Lean Body Mass with Severity of Metabolic Acidosis in Patients on Hemodialysis

Abstract

Background: Persistent metabolic acidosis (MA) in hemodialysis (HD) patients leads to protein breakdown, insulin resistance, and increased cardiovascular mortality. However, there is limited literature on the prevalence, determinants, and impact of MA in HD patients in India. We studied the association between protein intake and lean body mass (LBM) with the severity of MA in patients on regular HD. **Materials and Methods:** This single-center, cross-sectional study which enrolled patients >18 years on regular HD for at least 3 months. Normalized protein catabolic rate (nPCR) was measured, and protein intake was estimated using a diet diary. Urine nitrogen excretion was measured for 24 hours in patients with residual renal function, and the protein catabolic rate calculated from urea nitrogen excretion was added to the nPCR. LBM was estimated using the bioimpedance spectroscopy technique. **Results:** In 107 patients, 49.53% received HD twice a week; AV fistula was the vascular access for 96%, and CKDu was the most common CKD etiology. After HD, 94 (87.85%) patients had MA, and 26 (24.29%) had uncorrected acidosis; 82.05 and 62.9% of men and women had low LBM, respectively. Protein intake in our population was 0.45 ± 0.11 g/kg/day by diet diary and 0.73 ± 0.23 g/kg from nPCR. There was no significant association between LBM and protein intake with the severity of MA. **Conclusion:** Metabolic acidosis was common among HD patients but did not correlate with protein intake and LBM. Dietary protein intake was very low in HD patients.

Keywords: *Hemodialysis, Lean body mass, Metabolic acidosis, Normalized protein intake, Protein intake*

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DOI: 10.25259/IJN_378_2024

Received: 13-07-2024
Accepted: 19-11-2024
Online First: 20-02-2025
Published: ***

Supplementary available on: https://dx.doi.org/10.25259/IJN_378_2024

Introduction

It is estimated that about 200,000 people develop end-stage kidney disease (ESKD) in India every year, and 174,478 patients were on regular dialysis in 2018, with hemodialysis (HD) being the preferred modality in 94%.[1,2]

Most patients in India undergo HD twice a week, and low-flux dialyzers are still employed extensively. The outcomes of patients with HD remain poor, with mortality as high as 19% at the end of 2 years. The high mortality of patients with HD can be attributed to multiple factors such as cardiovascular disease, infection, and malnutrition. Malnutrition is common among HD patients in India[3] and may result from poor dietary intake due to persistent uremic state, metabolic acidosis (MA), and underprivileged socioeconomic background. In an earlier study, we reported that 73% of patients had persistent MA while on regular HD.[3,4] Persistent MA leads to protein breakdown, insulin resistance, worsening renal osteodystrophy, and increased cardiovascular mortality.[5–8]

With dietary habits and dialysis practices in India different from those of high-income countries, the prevalence and determinants of MA in dialysis patients are expected to differ from what is reported elsewhere. We studied the prevalence of MA in our dialysis population and its association with lean body mass (LBM) and dietary protein intake.

Materials and Methods

This single-center, cross-sectional observational study was done at the outpatient HD center at JIPMER, Puducherry from January 2019 to July 2020 after approval from the Institute Ethics Committee [IEC No.: JIP/IEC/2018/0153, dated 25/05/2018]. All adult (>18 years) patients under regular

How to cite this article: Nair GRG, Anand A, Rajappa M, Harinee M, Harichandrakumar KT, Priyamvada PS, et al. Association of Dietary Protein Intake and Lean Body Mass with Severity of Metabolic Acidosis in Patients on Hemodialysis. Indian J Nephrol. doi: 10.25259/IJN_378_2024

HD from our dialysis center for more than 3 months were offered participation in the study. Patients with any of the following were excluded: 1) any intercurrent illness during the 4 weeks preceding enrollment, 2) lack of reliable permanent vascular access in the form of a well-functioning AV fistula or permanent catheter, 3) limb amputation, 4) any evidence of chronic liver disease, ascites, significant pleural effusion, lung disease, poor compliance with dialysis treatment defined as skipping more than one session of HD in the preceding 4 weeks, and 5) acute or chronic kidney disease. The sample size was estimated with a sample correlation coefficient of 0.70 with a population value of 0.5 at a 5% significance level and 90% power. At any given point in time, approximately 105 patients are under regular HD at the dialysis center. Dialysis is offered in two shifts, six days a week. Initial screening was done for all patients, and among those who fulfilled the inclusion criteria, the first five in the daily dialysis roster during the recruitment stage were enrolled in the study. Their baseline characteristics were noted. A date for sample collection for serum bicarbonate, blood urea, and body composition analysis was fixed the following week, and a diet chart and a measuring cup for a diet diary were handed over to the patient. This procedure was repeated every day until the sample size was met.

Written informed consent was obtained from all the participants before enrollment. Demographic and clinical information, including dialysis prescriptions and medications, were collected at baseline.

The patient was interviewed by a qualified dietician and instructed to maintain a diet diary for 1 week. The patient was trained to quantify all items consumed in written or photographic form. The written material from the patient was collected at the end of 7 days. The dietician calculated daily dietary protein intake using the Indian Council of Medical Research (ICMR) data on the protein content of Indian food items. An average value was calculated to determine the protein intake of each patient.

Normalized protein catabolic rate (nPCR) was determined in all patients using the following formula: Protein Catabolic Rate = 0.22 + (0.036 × Interdialytic rise in BUN (midweek) × 24) / Interdialytic interval in hours. The protein catabolic rate calculated from urinary urea nitrogen using the formula urinary urea n(g) × 150/interdialytic interval (hours) × dry weight (kg) was added to the protein catabolic rate calculated from BUN to determine the actual (plasma + urine) protein catabolic rate in patients with residual renal function. A detailed description of nPCR and UUN calculations is provided in Supplementary Methods.

Serum bicarbonate levels were tested twice in all enrolled patients. A 1.0 mL venous sample was collected in a heparinized syringe from the AV fistula needle (arterial end) or the arterial limb of the dialysis catheter before dialysis treatment. At the end of the dialysis session, a second sample was collected from vascular access using a similar technique. The samples were transported after proper sealing and analyzed on a blood gas analyzer (Siemens RL-348Ex) in the Department of Nephrology without storing them. For patients on twice-a-week HD treatment, the bicarbonate levels were checked on the second treatment session (72 h between sessions). For patients on thrice-a-week treatment, the sampling was done on the mid-week dialysis session (48 h between sessions).

The dialysis dose delivered during the treatment session for which serum bicarbonate levels were checked and recorded from the online kt/v provided by the HD machine and measured kt/v was calculated by collecting pre- and post-dialysis samples for BUN. The post-dialysis sample for BUN was collected from the dialyzer inflow port using the slow flow technique by reducing blood flow to 100 mL/min for 15s. kt/v was calculated from these values using the Daugirdas equation to measure single pool kt/v.

The interdialytic weight gain between the previous session and the session during which the bicarbonate levels were tested was recorded. The sampling session was rescheduled if the weight gain was inconsistent with previous treatment sessions. All patients were asked to measure their urine output 24 hour before dialysis. Interdialytic weight gain was recorded during the session in which bicarbonate levels were tested.

The LBM was estimated using body composition monitoring (BCM) equipment using the bioimpedance spectroscopy technique (Fresenius Medical Care Pvt Ltd, Germany) post-dialysis on midweek dialysis day in patients who were on thrice-a-week dialysis and after the second dialysis session of the week in patients who were on twice-a-week dialysis. Lean tissue Index (LTI) was further calculated from LBM by normalizing for height. $LTI = LBM/Height^2$

Reports of lab tests performed within 30 days before enrollment in the study were collected from patient's records.

All our patients underwent a 4-hour HD session, with a blood flow rate of 250–300 mL/min and a dialysate flow rate of 500 mL/min. Dialysis was done by Fresenius 4008S machine (Fresenius Medical Care, Germany) with low-flux polysulfone dialyzers with a surface area of 0.8 to 1 × BSA.

Dialyzers were reused after mechanized reprocessing with Renatron® II 100 Series System, using Renalin (Medivators Inc., USA). Dialyzers were reused up to 10 times if the fiber bundle volume (FBV) was >80%. FBV was checked after each reprocessing, and the dialyzers were discarded if the FBV was less than 80%.

Statistical analysis was performed using SPSS version 22. The distribution of categorical variables such as age, gender, and clinical characteristics was expressed in terms of frequency and percentage. The distribution of continuous variables such as dialysis vintage, dialysis

characteristics, dietary protein intake, LBM, and serum bicarbonate was expressed in terms of mean with standard deviation, if normally distributed. Continuous variables that were not normally distributed were presented as medians with interquartile ranges (IQR). The categorical variables were compared using Pearson's chi-squared test or Fisher's exact test. The relationship between serum bicarbonate, LBM, and dietary protein intake was calculated by the Karl Pearson correlation coefficient if normally distributed, while Spearman's correlation test was used for non-normally distributed data. All statistical analysis was carried out at a 5% significance level, and a P-value less than 0.05 was considered statistically significant.

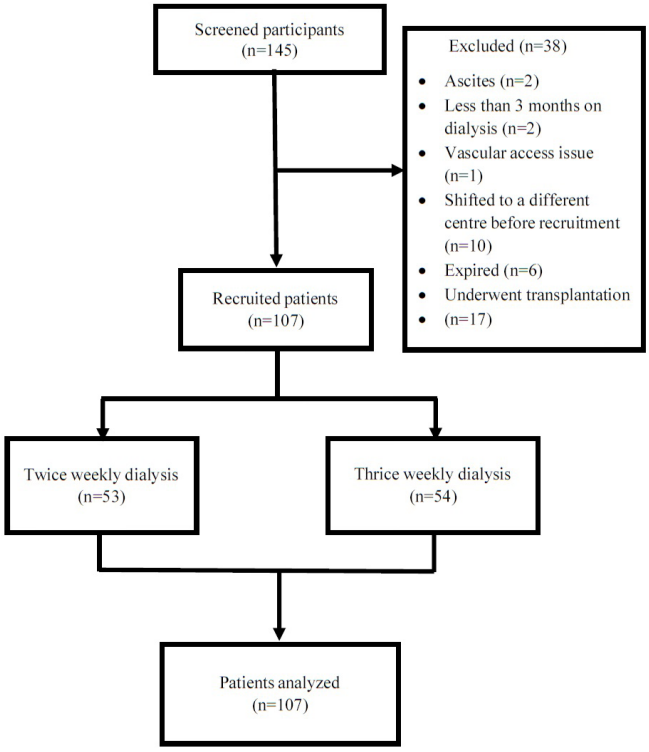

Figure 1: Study outline.

Results

Of 145 screened patients, 107 were enrolled [Figure 1]. A total of 79 patients (73.8%) were availing dialysis through government-sponsored insurance schemes, 22 (20.56%) were paying from their pockets for dialysis, and employers were bearing expenses for treatment in 6 (5.6%). The baseline characteristics of the study population are described in Table 1.

The most common etiology of CKD was CKDu (50.9%), followed by chronic glomerulonephritis (CGN 11.3%), chronic interstitial nephritis (CIN 5.7%), hypertensive nephrosclerosis (3.8%), and ADPKD (1.9%). Diabetic kidney disease accounted for only 13% of ESKD. A tunneled HD catheter was the vascular access in four (3.7%) patients, and everyone else had an AV fistula. Most patients (97.2%) were on diuretics, and 81.3% were on erythropoietin therapy [Supplementary Table 1].

Among 107 patients, 94 (87.85%) had MA when tested before their midweek dialysis session (in case of a thrice-a-week schedule) or before the session with longer interdialytic intervals (in case of a twice-a-week schedule). The predialysis pH was <7.35, indicating uncompensated MA in 60 patients (56.07%). Among those 60 patients, the proportion of uncompensated MA was similar between both groups; 28 (46.6%) patients were on thrice-weekly dialysis, whereas 32 (29.9%) patients were on twice-weekly dialysis. Three patients had metabolic alkalosis when tested before their scheduled dialysis treatment, with a pH > 7.45. The acid–base parameters are provided in Table 2 and Supplementary Table 2. The mean gain of bicarbonate at the end of dialysis in our study population was 7.43 ± 2.94 mEq/L.

The mean daily protein intake calculated from the diet diary in our study population was 0.45 ± 0.11 g/kg/day,

Table 1: Baseline characteristics

Parameters	Total n = 107	HD frequency 2 per week n = 53	HD frequency 3 per week n = 54	P value
Age (years)	40.3 ± 13.3	41.4 ± 14.5	39.2 ± 11.9	0.396
Female	29 (27.1%)	13 (24.5%)	16 (29.6%)	0.553
Duration of dialysis (years)	3.2 ± 1.8	3.1 ± 1.9	3.3 ± 1.6	0.628
Hypertension	107 (100%)	53 (100%)	54 (100%)	1.000
Diabetes mellitus	16 (15%)	9 (17%)	7 (13%)	0.560
Urine output (mL)	161.8 ± 283.6	251.7 ± 355.8	73.6 ± 143.8	0.001
SBP (mm Hg)	149.7 ± 15.3	147.19 ± 14.5	152.24 ± 15.8	0.090
DBP (mm Hg)	83.1 ± 13.4	81.6 ± 13.3	84.7 ± 13.4	0.240
Weight (kg)	57.1 ± 11.5	56.5 ± 8.8	57.7 ± 13.6	0.586
Interdialytic weight gain (kg)	2.3 ± 0.8	2.3 ± 0.7	2.3 ± 0.8	0.994
Online (kt/v)	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	0.016
Measured (kt/v)	1.6 ± 0.07	1.6 ± 0.2	1.6 ± 0.3	0.224
Dialysate bicarbonate (mEq/L)	34.2 ± 3.6	34.4 ± 3.6	34.1 ± 3.6	0.583
Hemoglobin (g/dL)	9.4 ± 2	9.4 ± 1.9	9.3 ± 2.1	0.764

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HD: Hemodialysis

Table 2: Acid–base parameters

Parameters	Total n = 107	HD frequency 2 per week n = 53	HD frequency 3 per week n = 54	P value
Pre-HD (pH)	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	0.621
Pre-HD PCO_2 (mmHg)	35.1 ± 7.2	34.4 ± 7.6	35.6 ± 6.8	0.396
Pre-HD bicarbonate, (mEq/L)	18.6 ± 2.8	18.2 ± 2.9	18.9 ± 2.7	0.172
Post-HD (pH)	7.4 ± 0.07	7.4 ± 0.06	7.3 ± 0.07	0.293
Post-HD PCO_2 (mmHg)	42.5 ± 9.3	39.7 ± 8.2	45.2 ± 9.5	0.002
Post-HD bicarbonate (mEq/L)	26.1 ± 2.9	26.4 ± 3.1	25.8 ± 2.7	0.199

HD: Hemodialysis, pCO_2: Partial pressure of carbon dioxide

and it was 0.73 ± 0.23 g/kg/day from nPCR. There was no significant difference in the dietary protein intake between patients on twice-a-week and thrice-a-week treatment schedules [Table 3]. There was no difference in the dietary protein intake between patients in the BPL category and others, whether it was intake estimated by diet diary (0.443 ± 0.09 in 2/week group vs 0.461 ± 0.12 in 3/week group; P = 0.252) or by nPCR (0.701 ± 0.19 in 2/week group vs 0.742 ± 0.23 in 3/week group; P = 0.583). Only 18 patients (16.82%) had serum albumin < 3.5 g/dL [Supplementary Table 3].

The mean LBM was low in 80% of the study population, that is 30.42 ± 6.77 kg [Supplementary Table 3]. The mean LBM in males was 31.96 ± 5.49 and that among females was 26.277 ± 8.11. The mean lean tissue index in our population was 11.56 ± 2.39 kg/m^2. However, no reference normal value of this is available for comparison with the Indian population. The serum albumin, phosphorus and iPTH values, and other nutritional parameters are provided in Table 3.

There was no statistically significant correlation between normalized protein catabolic rate (nPCR) (r = 0.091, P = 0.353), LBM (r = 0.136, P = 0.165), or protein intake (r = −0.022, P = 0.825) with predialysis serum bicarbonate levels. There was no correlation between predialysis serum bicarbonate levels and interdialytic weight gain (mL/kg) or online kt/v. There was a statistically significant positive correlation between serum albumin and LBM (r = 0.213, P = 0.028), and LBM and serum phosphorous in patients on thrice weekly dialysis [Supplementary Tables 4–6].

Discussion

We found that uncorrected MA was present in 87.85% of our HD patients. The dietary protein intake assessed by the diet diary and the estimated normalized protein catabolic rate were very low, and our patients had low LBM. There was no correlation between LBM and protein intake and the patients' severity of MA.

The KDOQI 2015 update on HD adequacy recommends that the predialysis serum bicarbonate measured before the midweek HD session should not be less than 22 mEq/L.[9] However, the prevalence of MA is reported to be 30–50% among patients on thrice-a-week of HD.[10,11] Midweek predialysis serum bicarbonate level appears to have a U-shaped association with patient survival, with bicarbonate levels less than 18 mEq/L and above 24 mEq/L associated with poor patient survival on maintenance HD.[12] It is a matter of concern that many of our patients had MA, and predialysis serum bicarbonate was less than 18 mEq/L in 39% of them.

The significant delay in measurement after collecting the sample, exposure to air, and the type of assay used may

Table 3: Comparison of nutritional parameters

Parameters	Total n = 107	HD frequency 2 per week n = 53	HD frequency 3 per week n = 54	P value
LBM (kg)	30.4 ± 6.7	30.2 ± 6.2	30.6 ± 7.3	0.761
Protein intake (g/kg/day)	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.263
nPCR (g/kg)	0.7 ± 0.2	0.6 ± 0.1	0.8 ± 0.2	0.060+
Albumin (g/dL)	3.9 ± 0.5	4 ± 0.5	3.9 ± 0.5	0.173
Phosphorus (mg/dL)	4.7 ± 1.5	4.9 ± 1.5	4.5 ± 1.5	0.282
iPTH (pg/dL)	452.6 ± 398.1	542.1 ± 424.7	363.2 ± 351.2	0.020
Calcium (mg/dL)	8.9 ± 0.7	8.9 ± 0.8	8.9 ± 0.6	0.875
ATM (kg)	26.7 ± 10.8	26.3 ± 10.2	27.1 ± 11.5	0.698
LTI (kg/m^2)	11.5 ± 2.4	11.5 ± 2.5	11.5 ± 2.3	0.953
Pre-HD BUN (mg/dL)	49.6 ± 14.5	53.8 ± 13.8	45.4 ± 14.1	0.003
UUN (mg/dL)	126.6 ± 46.2	138.3 ± 45.2	88.3 ± 24.4	0.010
Post-HD BUN (mg/dL)	14.5 ± 8.3	14.1 ± 8.1	15 ± 8.5	0.580

LBM: Lean body mass, nPCR: normalized protein catabolic rate, ATM: Adipose tissue mass, LTI: Lean tissue index, BUN: Blood urea nitrogen, UUN: Urinary urea nitrogen, HD: Hemodialysis

impact the measured bicarbonate level. We measured bicarbonate levels within 30 minutes of collecting the sample, and the assay was performed using a standardized blood gas analysis machine (Siemens RL-348Ex). Hence, it is unlikely that the errors in bicarbonate measurement contributed to the MA observed in our patients. The observations from our current study are consistent with the findings from our previous report on MA in HD and peritoneal dialysis patients at our center.[4]

Metabolic acidosis in ESKD patients on maintenance HD may be attributed to three factors: 1) low bicarbonate gains from dialysis caused by suboptimal dialysate bicarbonate level, 2) inadequate dialysis dose or skipping dialysis schedules, and 3) high dietary protein intake or gastrointestinal loss of bicarbonate.

None of our patients had any reason for excessive GI loss of bicarbonate. Protein intake was assessed in our patients using a diet diary, and the nPCR was measured. The protein content of Indian food items reported by ICMR[13] was used to estimate the protein intake from the diet diary. However, this method is fraught with problems because it depends on the patient's diet documentation.[14] Hence, we also estimated the protein intake using the nPCR, including the urinary clearance of urea nitrogen. Protein intake was low in all patients in our study, with no patients meeting the recommended dietary protein intake of 1.2 g/kg/day [Supplementary Table 3]. Dietary protein intake is reported to be low in Indians, even when they report to be nonvegetarians.[15] Rao *et al*. reported that protein and calorie intake was low in dialysis patients at their center in South India. The intake of both calories and protein worsened with a longer dialysis vintage.[16] Kamat *et al*. reported that dietary protein intake was very low among HD patients at their center in Mumbai, with only 20% having a protein intake of more than 0.8 g/kg/day.[17] Our patients were mostly from an underprivileged background, which could contribute to the low dietary protein intake. Socioeconomic factors are known to be associated with ESKD risk and death in patients with CKD. Modi *et al*. reported that socioeconomic factors, including lower education and lower income, were negatively associated with reduced health-related quality of life in CKD in India.[18,19] High protein intake is known to contribute to MA. Since the protein intake of our patient population was extremely low, it may be inferred that dietary protein intake was not the primary reason for MA.

Serum bicarbonate level in the dialysate at our outpatient HD center was maintained at 34 mEq/L. This is consistent with the practice in most dialysis centers in India. The mean dialysate bicarbonate concentration was 32.2 $\pm$ 2.3 meq/L in Germany and 37.0 $\pm$ 2.6 mEq/L in the USA. Individualized prescriptions of dialysate bicarbonate are not universally practiced in HD centers. A nonindividualized prescription (the same bicarbonate for all patients) was followed by 76% of dialysis centers in the United Kingdom and 54% in the USA.[20] Besides bicarbonate (alkali) gained during HD sessions, factors such as protein intake, dialysis dose, and tissue catabolism are key determinants of MA in dialysis patients. We demonstrated an average bicarbonate gain of 7.43 $\pm$ 2.94 mEq/L. During an HD session, most of the alkali gain happens in the first 2 hours, with very little gain over the remaining duration of dialysis.[5] Our patients received a standard treatment duration of 4 h. Hence, the MA in our dialysis patients cannot be attributed to inadequate dialysate bicarbonate levels.

We employed a standard HD prescription; >96% had AV fistula as vascular access, and the dialyzer used was appropriate for the body surface area of patients. We routinely monitor solute clearance (online clearance monitoring) at our dialysis center. Though the dialysis dose assessed by online clearance was suboptimal, the mean measured spkt/v was 1.6. Al Saran *et al*. reported a similar discordance between online clearance monitoring and actual measured solute clearance, where the mean online kt/v was 1.02. In contrast, the calculated kt/v was 1.37.[21]

It is challenging to explain the MA observed in our patients, despite the adequate dialysis prescription (measured kt/v) and the lack of other contributing factors. This warrants further study including whether a very low dietary protein intake leads to a catabolic state with worsening MA.[22]

We could not find any correlation between LTM, nPCR, and severity of MA (serum bicarbonate level) in our patients. A higher LTM, nPCR, and interdialytic weight gain are negatively correlated to serum bicarbonate levels in HD patients.[23] We believe that a larger sample size might have revealed any association between LTM, nPCR, interdialysis weight gain, and serum bicarbonate levels.

The mean age of our study population was 40.35 $\pm$ 13.30, which is at least 20 years less than the average age of patients on dialysis in the USA (64 years) or the UK (67 years).[24] This is comparable with other Indian centers.[25] In addition to being significantly younger, more than 90% of them had AV fistula as vascular access for dialysis, and the prevalence of diabetes mellitus was low. All these are factors associated with better patient outcomes on dialysis.[26–28] However, these patients had a low dietary protein intake and LTM, and persistent and severe MA, which were associated with poor outcomes.

The nPCR in patients on thrice-a-week HD schedule was numerically higher than those on twice-a-week HD. Post hoc power calculation with 0.05 alpha level was 100%, suggesting this difference was likely significant. This suggests that a higher dialysis dose (weekly kt/v) was likely associated with a higher nPCR in our patient population, and increasing the dialysis dose may result in a higher dietary protein intake.

Even though we could not find a correlation between protein intake, LBM, and severity of MA, the study provided some important insights. Most importantly, the very low protein intake among HD patients is a cause of concern, given the strong association between dietary protein intake, malnutrition, and outcomes in HD patients. Despite following an HD prescription consistent with the prevailing dialysis practices in many dialysis centers in India and with 50% of patients on a thrice-a-week HD schedule, MA was the norm among HD patients. These observations emphasize the need to review existing HD practices and explore cost-effective ways to improve dialysis dose and dietary protein intake among our HD patients.

In conclusion, persistent metabolic acidosis is common among patients undergoing regular HD and remains uncorrected even after dialysis in a significant proportion of patients. Dietary protein intake and LBM were low in our patients. There was no correlation between LBM and protein intake and severity of MA.

Financial support and sponsorship: Intramural research grant from JIPMER, Puducherry.

Conflicts of interest: There are no conflicts of interest.

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