Prevalence and Predictors of Vitamin B6 Deficiency in Hemodialysis Patients Not Receiving Vitamin Supplementation

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ABSTRACT **Background:** Vitamin B6 is an essential cofactor in amino acid metabolism. Its deficiency is linked to neuropathy, anemia, and cardiovascular risk. Deficiency is common among hemodialysis patients due to dialytic losses and restrictive diets; however, data related to high-flux (HF) dialysis membranes and Mediterranean dietary patterns are scarce.

Objectives: To assess the prevalence and determinants of deficiency in unsupplemented Israeli hemodialysis patients.

Methods: This retrospective chart review, utilizing a cross-sectional design, was conducted in August 2024. We included 27 chronic hemodialysis patients not receiving vitamin B6 supplementation, representing the available unsupplemented cohort from a unit of approximately 150 patients. Vitamin B6 status was assessed by measuring plasma pyridoxal-5'-phosphate (PLP); deficiency < 20 ng/ml. Clinical and nutritional parameters were evaluated to identify deficiency.

Results: Vitamin B6 deficiency was noted in 63% of patients (median PLP 18 ng/ml, interquartile range 13–23). The cohort was 67% male, median age 74 years. All patients were treated with HF dialyzers. No significant correlations were found between PLP levels and nutritional indices or laboratory markers. A non-significant trend was observed between older age and lower PLP levels ($r = -0.35$, $P = 0.098$).

Conclusions: Vitamin B6 deficiency was common among Israeli hemodialysis patients treated with HF dialyzers, despite a presumed Mediterranean diet. It was not associated with nutritional status, suggesting dialysis-related losses, potentially augmented by high-flux membranes, may outweigh intake. Given the high prevalence of deficiency and low cost, routine low-dose vitamin B6 supplementation may be warranted, particularly in older patients.

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KEY WORDS: high-flux dialyzer, Mediterranean diet, micronutrient, pyridoxal-5'-phosphate (PLP), vitamin B6

Vitamin B6 serves as an essential cofactor in multiple enzymatic reactions related to amino acid metabolism. In the human body, it exists primarily as pyridoxal, pyridoxamine, and pyridoxine, with pyridoxal-5'-phosphate (PLP) as the active metabolic form [1]. While vitamin B6 deficiency affects only about 3% of the healthy population [2,3], it is significantly more prevalent among hemodialysis patients due to several disease-specific factors. In this population, deficiency is driven by restrictive diets [4], interactions with medications such as erythropoiesis-stimulating agents (ESA) or phosphate binders [5], and significant dialytic losses. Among water-soluble vitamins, B6 is particularly vulnerable due to its small molecular size and limited body reserves [1]. While high-flux dialyzers are often cited as a primary cause of increased clearance [6], some evidence suggests that acute vitamin B6 loss may be an inherent feature of the dialysis process itself, regardless of membrane flux [7,8].

Deficiency may manifest as weakness, irritability, and sleep disturbances, as well as peripheral neuropathy, seborrheic lesions on the skin, anemia, and increased cardiovascular risks [9,10]. Studies published in the 1990s and the early 2000s reported deficiency in up to half of hemodialysis patients not receiving supplementation, but these data may not reflect current dialysis practice. Despite recommendations for 10 mg/day supplementation [11], data from Israel are lacking, and until recently the only available supplement (Tribemin, Sam-On Ltd. [Meditech], Bat Yam, Israel) contained 250 mg, substantially exceeding recommended daily doses. Most studies evaluating vitamin B6 status in hemodialysis patients were conducted more than two decades ago, before the widespread adoption of modern high-flux dialysis and contemporary dietary patterns such as the Mediter-

ranean diet, which is characterized by an abundance of vitamin B6-rich sources. Therefore, in this study, we assessed the prevalence and determinants of vitamin B6 deficiency in unsupplemented hemodialysis patients in Israel.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

This retrospective chart review, utilizing a cross-sectional design, was conducted at the Meir Medical Center hemodialysis unit, which serves approximately 150 chronic patients [12,13]. In August 2024, we identified 27 patients (≥ 18 years) who had been undergoing high-flux hemodialysis for at least 3 months and were not receiving vitamin B6 supplementation at the time of the study or within the preceding 6 months. The lack of supplementation reflected a historical absence of standardized clinical protocols rather than specific medical indications. This group comprised the entire available cohort of unsupplemented patients within the unit during the study period, providing a unique opportunity to assess endogenous PLP levels in a contemporary hemodialysis population.

DATA COLLECTION

Demographic, clinical, and dialysis-related data were extracted from electronic medical records. This information included patient co-morbidities, dialysis vintage, and laboratory results obtained on the day of PLP measurement. Data regarding dialyzer types and weekly dialysis hours were also recorded. Laboratory samples were collected at the start of a mid-week hemodialysis session.

ETHICS CONSIDERATIONS

The study was approved by the Institutional Ethics Committee of Meir Medical Center (0091-24-MMC). Informed consent was waived due to the retrospective, anonymized study design.

NUTRITIONAL AND DIALYSIS PARAMETERS

The malnutrition-inflammation score (MIS) score is a validated, semi-quantitative tool commonly used for patients undergoing dialysis to assess the severity of protein-energy wasting and inflammation [14,15]. The normalized protein catabolic rate (nPCR) is an estimate of protein intake, derived from pre- and post-dialysis blood urea nitrogen [16]. Kt/V is an index used to assess dialysis adequacy, reflecting the fractional removal of urea during a dialysis session.

Nutritional status was further evaluated by the unit's dietitian team through structured interviews and the subjective global assessment (SGA). This comprehensive review integrated daily caloric and protein intake (including g/kg) against estimated energy expenditure, gastrointestinal symptoms, and changes in dietary habits. In addition, weight history was analyzed to determine absolute and percentage weight loss, while physical exams tracked muscle and fat trends, longitudinally. Based on this integration, patients were classified as having normal nutrition or mild or severe malnutrition.

PYRIDOXAL-5'-PHOSPHATE MEASUREMENT

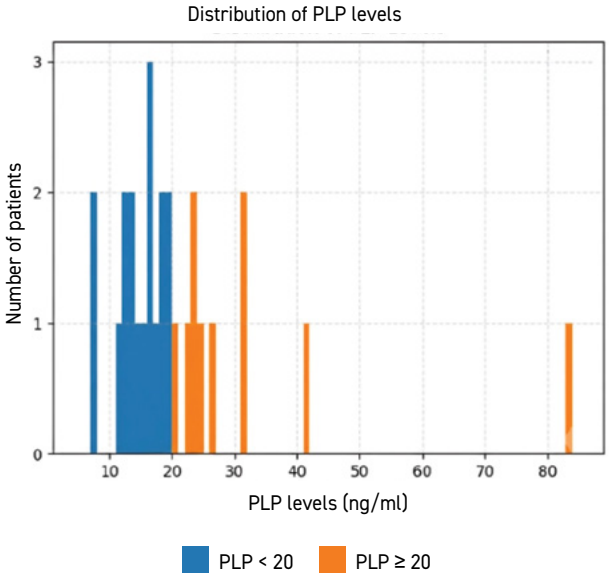
Total body vitamin B6 status was evaluated by measuring PLP, which is considered the most reliable indicator of vitamin B6 levels. In accordance with widely accepted clinical literature, vitamin B6 deficiency was defined as a PLP level below 20 ng/m. PLP was measured in blood samples collected at the start of the hemodialysis session.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 29 (SPSS, IBM Corp, Armonk, NY, USA). The normality of

Figure 1. Pyridoxal-5'-phosphate levels in the patient population

Distribution of PLP levels: The median PLP was 18 ng/ml, range 8–83 ng/ml
Vitamin B6 deficiency refers to PLP level < 20 ng/ml (blue) and vitamin B6 sufficiency refers to PLP level ≥ 20 ng/ml (orange)
PLP = pyridoxal-5'-phosphate



data distribution was assessed using the Shapiro-Wilk test. Continuous variables are presented as mean ± SD for normally distributed data, and as median (interquartile range [IQR]) for non-normally distributed variables. To compare continuous variables between patients with or without vitamin B6 deficiency, the Mann-Whitney U test was applied, as most parameters demonstrated a non-normal distribution or were analyzed within a small sample size. Fisher's exact test was used to compare categorical variables between the two groups. Correlations between PLP levels and clinical/laboratory parameters were evaluated using Spearman's rank correlation coefficient to account for non-normal distributions and the small sample size. A P-value < 0.05 was considered statistically significant.

USE OF ARTIFICIAL INTELLIGENCE TOOLS

Artificial intelligence (AI)-based tools were used to assist with language editing of the manuscript after its initial drafting. In addition, Figure 1 was generated using AI tools. The use of these tools was limited to language editing and figure generation and did not influence the scientific content or data interpretation.

RESULTS

Among 150 chronic hemodialysis patients, 27 met the inclusion criteria. The median age was 74 (IQR 64–84), and 67% were male. Major co-morbidities included hypertension (89%), diabetes mellitus (52%), and ischemic heart disease (48%) [Table 1]. The leading causes of end-stage kidney disease were diabetes mellitus (37%) and hypertension (19%). Nutritional assessment showed a mean body mass index (BMI) of 26 ± 5.5 kg/m², mean MIS score of 15.1 ± 4.0, and mean nPCR of 0.94 ± 0.26. The median dialysis vintage was 18 months (IQR 7–50), with an average of 11.5 hours/week of treatment. All

Table 1. Demographic, clinical, and laboratory characteristics of the study patients (N=27)

Patient demographics	Values	Patient demographics	Values
Age (years)*	74 (64–84)	Severe malnutrition	3 (11%)
Sex (male)	18 (67%)	**Dialysis data**	
Patient co-morbidities		Weekly dosage (hours)	11.5 ± 1.96
Hypertension	24 (89%)	Dialysis vintage (months)*	18 (7–50)
Diabetes mellitus	14 (52%)	Kt/V	1.39 ± 0.35
Malignancy	3 (11%)	**Dialyzer type**	
Peripheral vascular disease	8 (30%)	Revaclear 400/500	4 (15%)
Atrial fibrillation	8 (30%)	FX 80\100	23 (85%)
Ischemic heart disease	13 (48%)	**Laboratory results**	
Heart failure	10 (37%)	Urea (mg/dl)	111.7 ± 38.3
Primary renal disease		Creatinine (mg/dl)	6.1 ± 2.1
Diabetes	10 (37%)	Albumin (g/dl)	3.6 ± 0.4
Hypertension	5 (19%)	Calcium (mg/dl)	8.4 ± 0.6
Other	5 (19%)	Phosphate (mg/dl)	4.8 ± 1.6
Unknown	7 (26%)	Parathyroid hormone (pg/ml)*	319 (152–501)
Nutritional status		Glucose (mg/dl)*	128 (100–158)
BMI kg/m²	26 ± 5.5	CRP (mg/dl)*	0.8 (0.4–1.9)
MIS score	15.1 ± 4.0	Hemoglobin (g/dl)	10.5 ± 1.5
nPCR	0.94 ± 0.26	Iron (µg/dl)	54.9 ± 27.1
Nutritional assessment		TIBC score (µg/dl)	202.3 ± 41.6
Normal nutrition	17 (63%)	B12 (pg/ml)*	571.0 (382–806)
Mild malnutrition	7 (26%)	Folic acid (ng/ml)	17.4 ± 8.2

Continuous variables are presented as mean ± SD or *median (interquartile range), as appropriate. Categorical variables are presented as absolute number, %. Nutritional assessment is classified via the Subjective Global Assessment (SGA) and dietitian-led clinical review, incorporating dietary intake (caloric/protein), weight loss history, gastrointestinal symptoms, and physical assessment of body composition.
In Kt/v equation, K is the dialyzer clearance of urea, t is dialysis time, and v is volume of distribution of urea, approximately equal to the patient's total body water.
BMI = body mass index, MIS = malnutrition-inflammation score, nPCR = normalized protein catabolic rate, CRP = C-reactive protein, TIBC = total iron-binding capacity

patients were treated exclusively with high-flux dialyzers, consisting of FX-class 80/100 (85%) or Revaclear 400/500 (15%) (Baxter, Deerfield, IL, USA).

PYRIDOXAL-5'-PHOSPHATE LEVELS

The median PLP was 18 ng/ml (IQR 13–23; range 8–83 ng/ml). Vitamin B6 deficiency (PLP level < 20 ng/ml) was identified in 17 patients (63%), while the remaining 10 patients (37%) had adequate PLP levels [Figure 1].

ASSOCIATION BETWEEN DEMOGRAPHIC, CLINICAL AND LABORATORY PARAMETERS, AND PLP LEVELS

Spearman's rank correlation analysis revealed no significant associations between PLP levels and the study parameters [Table 2]. Specifically, no significant correlations were found with nutritional markers, including MIS (r = -0.24, $P = 0.21$), nPCR (r = 0.05, $P = 0.8$), serum creatinine (r = 0.16, $P = 0.40$), albumin (r = 0.01, $P = 0.95$), or CRP (r = -0.05, $P = 0.78$). A trend was noted between older age and lower PLP levels (r = -0.35, $P = 0.098$).

COMPARISON BETWEEN PATIENTS WITH ADEQUATE AND DEFICIENT PLP LEVELS

No significant differences were observed between the adequate (n=10) and deficient (n=17) groups across the evaluated nutritional and laboratory markers, including B12 and folate levels. Similarly, analysis of categorical variables and dialysis-related parameters [Table 3] showed no significant association between vitamin B6 status and patient sex ($P = 0.21$), co-morbidities ($P > 0.05$), or the use of specific medications such as ESA ($P = 0.61$) and phosphate binders ($P = 0.2$).

Table 2. Spearman's rank correlation between demographic, clinical, and laboratory parameters, and PLP levels

Variable	Spearman's rho	*P*-value
Demographic characteristics		
Age	-0.35	0.098
Nutritional parameters		
MIS score	0.24-	0.21
nPCR	0.05	0.80
BMI	0.19	0.33
Dialysis characteristics		
Dialysis vintage (months)	0.21	0.29
weekly dosage (hours)	0.10	0.60
Kt/v	0.09	0.66
Laboratory		
Urea (mg/dl)	0.04	0.82
Creatinine (mg/dl)	0.16	0.40
Albumin (g/dl)	0.01	0.95
Calcium (mg/dl)	-0.15	0.45
Phosphate (mg/dl)	0.03	0.86
Parathyroid hormone (pg/ml)	-0.27	0.15
Glucose (mg/dl)	0.29	0.14
CRP (mg/dl)	-0.05	0.78
Hemoglobin (g/dl)	0.08	0.68
Iron (µg/dl)	-0.03	0.88
TIBC (µg/dl)	0.04	0.83
B12 (pg/ml)	0.13	0.49
Folic acid (ng/ml)	-0.20	0.30

In the Kt/v equation, K is the dialyzer clearance of urea, t is dialysis time, and v is volume of distribution of urea, approximately equal to the patient's total body water.
Correlations were performed using Spearman's rank correlation coefficient due to the non-normal distribution of PLP levels.
BMI = body mass index, MIS = malnutrition-inflammation score, nPCR = normalized protein catabolic rate, CRP = C-reactive protein, TIBC = total iron-binding capacity

DISCUSSION

In this study, we evaluated plasma PLP concentrations in unsupplemented chronic hemodialysis patients in Israel. The most striking finding was that vitamin B6 deficiency was present in 63% of the patients (median PLP 18 ng/ml). This high prevalence was not expected, as the cohort consisted of clinically stable, chronic patients with a relatively preserved nutritional status, reflected by a mean BMI of 26 kg/m², normal serum albumin levels (mean 3.6 g/dl), and nutritional assessments that did not indicate malnutrition in most of the patients. We anticipated that vitamin B6 status in the cohort would be primarily determined by the interplay between overall nutritional status and dietary patterns and would therefore be relatively well-preserved. Regarding diet and nutrition, the initial hypothesis suggested that a Mediterranean diet, abundant in vitamin B6-rich sources, combined with stable nutritional parameters, might offer a protective effect. However, the findings diverged from this expectation, as the observed 63% PLP deficiency rate notably exceeded the 33–56% range reported in landmark studies [11].

Consistent with this finding, the analysis showed no significant association between plasma PLP levels and comprehensive nutritional indices of MIS, nPCR, and SGA or laboratory markers [17]. This result implies that the potential benefits of a Mediterranean diet may be outweighed by other factors influencing PLP concentrations

Table 3. Association between categorical variables and PLP status

Characteristic	PLP adequate (n=10)	PLP deficiency (n=17)	*P*-value
Sex			
Male	5 (50.0%)	13 (76.5%)	0.21
Female	5 (50.0%)	4 (23.5%)	
Dialyzer type			
400/500	1 (10%)	3 (18%)	1.00
FX 80/100	9 (90%)	14 (82%)	
Congestive heart failure			
Yes	4 (40.0%)	6 (35.3%)	1.00
No	6 (60.0%)	11 (64.7%)	
Hypertension			
Yes	8 (80.0%)	16 (94.1%)	0.53
No	2 (20.0%)	1 (5.9%)	
Diabetes mellitus			
Yes	6 (60.0%)	8 (47.1%)	0.69
No	4 (40.0%)	9 (52.9%)	
Ischemic heart disease			
Yes	5 (50.0%)	8 (47.1%)	1.00
No	5 (50.0%)	9 (52.9%)	
Peripheral vascular disease			
Yes	4 (40.0%)	4 (23.5%)	0.41
No	6 (60.0%)	13 (76.5%)	
Cinacalcet			
Yes	5 (50.0%)	7 (41.2%)	0.70
No	5 (50.0%)	10 (58.8%)	
Phosphate binder treatment			
Yes	8 (80.0%)	9 (52.9%)	0.20
No	2 (20.0%)	8 (47.1%)	
Vitamin D treatment			
Yes	6 (60.0%)	11 (64.7%)	1.00
No	4 (40.0%)	6 (35.3%)	
Erythropoiesis-stimulating agents			
Yes	9 (90.0%)	12 (70.6%)	0.61
No	1 (10.0%)	5 (29.4%)	
Cobalamin treatment			
Yes	1 (10.0%)	2 (11.8%)	1.00
No	9 (90.0%)	15 (88.2%)	
Folate treatment			
Yes	5 (50.0%)	8 (47.1%)	1.00
No	5 (50.0%)	9 (52.9%)	

**P*-values were calculated using Fisher's exact test

in hemodialysis patients. Regarding dialytic clearance, the results underscored the dominant role dominant role of modern dialysis technology. While earlier landmark studies often included patients on low-flux dialysis [7,18], the present cohort was treated exclusively with modern high-flux membranes, which maximize the convective clearance of water-soluble vitamins. The 63% deficiency rate we observed is aligned with the upper end of the spectrum reported in high-flux cohorts [18], supporting the trade-off inherent to these membranes. Prior research indicates that high-efficiency dialyzers can reduce plasma PLP levels by half within months, even with supplementation [18], and can cause acute washout of up to 48% per session [8]. However, the reports in the literature remain somewhat inconsistent. Some studies have suggested that acute vitamin B6 loss may be an inherent characteristic of the dialysis process itself, occurring independently of membrane flux [7,8]. This thought is further supported by data from advanced modalities like online hemodiafiltration, which combines diffusion with high-volume convection to maximize solute clearance, where the additional loss of water-soluble vitamins is not necessarily greater than in conventional high-flux hemodialysis [5]. These differences suggest that vitamin levels are affected by factors other than membrane permeability. Larger controlled studies are needed to clearly understand the role of membrane flux.

A non-significant trend toward lower PLP levels in older patients ($r = -0.35$, $P = 0.098$) is supported by reports attributing B6 deficiency in the elderly to reduced absorption and intake [19]. Given the median age of 74 years in our cohort, these findings suggest that the threshold for clinical suspicion and intervention should be particularly low in elderly hemodialysis patients.

Therapeutic factors, such as phosphate binders and ESA, have been suggested to negatively impact vitamin B6 status [20]. While the analysis did not find evidence of these interactions, the result was likely due to the limited statistical power of the small cohort (n=27), and particularly the few patients not receiving ESA.

Unlike vitamin B6, vitamin B12 and folate levels remained within the normal range. This finding may be explained by several factors, including routine supplementation in many dialysis patients, greater dietary availability, lower dialytic clearance compared with vitamin B6 [1,20], and the presence of substantial body stores of vitamin B12. Given the high prevalence of deficiency observed, the findings presented here support the recommendation to add routine, low-dose vitamin B6 supplementation as a practical strategy for hemodialysis patients.

LIMITATIONS

First, the small sample size (n=27) limited statistical power; therefore, multivariable analysis was not performed. In addition, the cohort represents a subset of patients who did not receive routine vitamin B6 supplementation prior to protocol standardization, which may introduce selection bias. Second, the cross-sectional design precluded causal inference. Last, dietary intake was not directly assessed using validated questionnaires, limiting conclusions regarding adherence to Mediterranean dietary patterns.

CONCLUSIONS

In this study, we found a high prevalence of vitamin B6 deficiency (63%) in a cohort of Israeli hemodialysis patients; all treated with high-flux dialyzers. Notably, a significant correlation with overall nutritional status was not observed. This risk appears particularly high in elderly patients, where a trend toward lower PLP levels was observed. While the small sample size warrants caution, these results highlight the strong risk for deficiency in this population. Given the significant cost of plasma PLP assays compared to the low cost and safety profile of vitamin B6 measurements, the findings support the recommendation for routine, low-dose supplementation of vitamin B6 for hemodialysis patients.

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Words are the only things that last forever; they are more durable than the eternal hills.
William Hazlitt (1778–1830), English essayist, drama and literary critic, painter, social commentator, and philosopher