Vol 2 | Issue 1 | Pages 58-64

Journal of Human Nutrition
ISSN: 2642-4878

Research Article

DOI: 10.36959/487/282

Factors Contributing to the High Prevalence of Vitamin B6 Deficiency in US: A Systematic Review

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Abstract

Objective: Based on the "Second National Report on Biochemical Indicators of Diet and Nutrition in the US Population" from CDC in 2012, 10.5% of the population over 1-year-old were vitamin B6 deficient (plasma pyridoxal 5'-phosphate < 20 nM). We hypothesize that gender, age, food preparation, and disease conditions could affect the intake and/or the availability of vitamin B6.

Methods: Literature review was performed to test the hypothesis. MEDLINE, PubMed, Web of Science and Google were used. Only papers that reported biochemical indicators of B6 status were used in analyzing B6 deficiency.

Results: Most studies collected B6 intake information through the dietary recall method. Among healthy populations over 1-year-old from different countries, women (especially those with restricted energy intake) and older adults tended to have lower intake than RDA and thus experienced a higher incidence of deficiency. About half of the nursing home residents showed B6 deficiency. Even in the populations with mean intake higher than RDA, deficiency persisted in up to 20% of the individuals. Lower functional bioavailability of B6 from plant origins or the loss of functional B6 during storage and cooking could negatively affect B6 status. B6 deficiency was also studied among patients with chronic diseases. Patients with type 2 diabetes, colorectal cancer, rheumatoid arthritis, renal disease and renal transplant showed various degrees of B6 deficiency. Renal dialysis likely led to increased B6 depletion through reduced renal reabsorption and thus a 100% B6 deficiency was observed in patients before B6 supplementation. B6 deficiency in Type 2 diabetes could also be due to a higher renal loss. In addition, increased catabolism and intracellular retention may contribute to the low plasma pyridoxal 5'-phosphate levels among patients with inflammatory conditions.

Conclusions: Intake below requirement (due to lower energy intake) and disease conditions (especially renal diseases) are risk factors for B6 deficiency. Screening for B6 deficiency and B6 supplementation may be necessary for these at-risk populations.

Introduction

Vitamin B6 has a wide range of nutritional importance. The active coenzyme form of vitamin B6, pyridoxal-phosphate (PLP), is associated with more than one hundred enzymes. It participates in biochemical reactions including the amino acid and homocysteine metabolism, cellular multiplication, glucose and lipid metabolism, neurotransmitter production, DNA/RNA synthesis and gene expression modulation [1-3].

The metabolism, absorption and intracellular trafficking of vitamin B6 have been reviewed [4,5]. Major biological forms of vitamin B6 are pyridoxine (PN), pyridoxal (PL) and pyridoxamine (PM). After passively absorbed in the intestine, vitamin B6 is converted to PLP for function. Plasma PLP is a convenient and most frequently used biomarker of vitamin B6 status [3,4,6]. Vitamin B_6 deficiency is diagnosed when plasma PLP level is lower than 20 nmol/L. Suboptimal vitamin B_6 status may be considered when plasma PLP concentrations are at 20-30 nmol/L [7].

The hepatic catabolic product of B6, 4-pyridoxic acid (PA), is excreted in the urine and has also been used as an indicator of recent vitamin intake [4]. Urinary PA excretion of ≤ 3.0 μmol/day is thought to indicate deficiency. In addition, plasma PL plus PLP, and plasma ratio of PA to PL plus PLP have been used as indicators of B6 status as reviewed before [4]. Because PLP is needed for various biochemical reactions, B6 functional status can also been determined through the activity of PLP-dependent enzymes, for example, aminotransferase activities in the erythrocyte and plasma kynurenine metabolites [4].

When plasma level of PLP was used by The Centers for

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Accepted: December 29, 2018:

Published online: December 31, 2018

Citation: Tang Y, Xu M, Shiu-Ming K (2018) Factors Contributing to the High Prevalence of Vitamin B6 Deficiency in US: A Systematic Review. J Hum Nutr 2(1):58-64

Disease Control and Prevention (CDC) in the analysis of data from 2003-2006 National Health and Nutrition Examination Survey (NHANES), over 10% of US population over 1-year-old was found to be vitamin B6 deficient (plasma PLP < 20 nmol/L) (http://www.cdc.gov/nutritionreport). This "Second National Report on Biochemical Indicators of Diet and Nutrition in the US Population" issued by CDC in 2012 actually found B6 deficiency to be the most common nutrient deficiency. Using various indicators of B6 status as mentioned above, chronic suboptimal B6 status has been linked to increased risks for cardiovascular diseases [8,9], and cancers [6,10-12].

While low vitamin B6 intake can lead to deficiency, plasma level of PLP did not always strongly correlate to the estimated vitamin B6 intake in population studies [4]. Other factors may also affect the metabolism of vitamin B6 and increase the incidence of vitamin B6 deficiency. Compared to other micronutrients that were also identified in the CDC report as showing deficiency in US, vitamin B6 has not been studied as much. This review summarizes the available observations on vitamin B6 status. We hypothesize that gender, age, food preparation, and disease conditions could affect the availability and/or the metabolism of vitamin B6. The identification of risk factors for vitamin B6 deficiency is an essential step in promoting proper vitamin B6 nutrition.

Methods

Literature review was performed to test the hypothesis. MEDLINE, PubMed, Web of Science and Google were used to identify articles published from 1971 to 2017 using the keywords "vitamin B6 deficiency", "vitamin B6 deficiency diseases", "PLP deficiency", and "plasma PLP level", "vitamin B6 food sources and /or storage". Only papers that reported biochemical indicators of B6 status were used in analyzing B6 deficiency.

Results and Discussion

The literature review uncovered several possible causes of vitamin B6 deficiency in the population as described below.

Lower B6 intake than the Recommended Dietary Allowance (RDA)

A good correlation between B6 intake and plasma PLP was reported in some studies [7]. We summarized studies on the relationship between B6 intake and B6 status among healthy individuals in Table 1.

Vitamin B6 is present in almost all foods. Low overall food intake is a risk factor for poor B6 status. In addition, the RDA of vitamin B6 ranges from 0.1 mg (newborns) to 2

Table 1: Summary of vitamin B6 deficiency that can be explained by low intake.

Subjects	Dietary measurement	Mean vitamin B6 intake (mg/d)		RDA (mg/d)		Vitamin B6 deficiency group	Measurement of vitamin B6	References
300 Dutch adults (20 - 79y)	3-day dietary record	Men (20 - 49y)	1.67 ± 0.45	1.30		Based on plasma PLP: 16% deficiency among men age 50 - 79y, other groups, 3 - 7% deficiency; Based on functional status parameters: 0 - 8% deficiency	Plasma PLP, Plasma PL + PLP, urinary 4-PA, erythrocyte alanine and aspartate aminotransferase activities (EALT-AC and EAST-AC)	[13-15]
		Men (50 - 79y)	1.39 ± 0.40	1.70				
		Women (20 - 49y)	1.19 ± 0.54	1.30				
		Women (50 - 79y)	1.15 ± 0.24	1.50				
103 healthy Taiwan adolescents (13 - 15y)	3-day dietary recall	Boys	1.04 ± 0.24	1.30		No plasma PLP < 20 nmol/L but 4% boys and 17% girls urinary 4-PA < 3 µmol/d	Plasma PLP, urinary 4-PA, erythrocyte alanine and aspartate aminotransferase activities (EALT-AC and EAST-AC)	[16]
		Girls	0.83 ± 0.26	1.20				
		19-30y	1.50 ± 0.30	1.30				
6159 participants of NHANES (> 1y)	2-day 24h dietary recall	nonusers of supplements	1.86 ± 0.02	0.50 - 1.70		Deficiency in 11% of supplement users, 24% of nonusers; highest deficiency among age 21 - 44y	Plasma PLP	[17]
		supplement usuers	1.94 ± 0.02					
1236 Puerto Rican adults (45 - 75 years)	Dietary recall	Men	2.46 ± 0.98	31-50y	1.30	22.5% women and 19.3% men not meeting RDA; 11% plasma PLP < 20 nmol/L, and 17% < 30 nmol/L	Plasma PLP	[18]
				> 51y	1.70			
		Women	2.19 ± 0.96	31 - 50y	1.30			
				> 51y	1.50			
61 nursing home residents (85.3 ± 6.8y)	Weekly dietary recall	Men	1.60 ± 0.30	1.70		49% deficiency	Plasma PLP	[19]
		Women	1.18 ± 0.31	1.50				

254 Korean adults (20 - 64y)	3-day 24h dietary recall	Men	2.17 ± 0.67	1.30 - 1.70	15.7% plasma PLP < 20 nmol/L; 35.4% < 30 nmol/L	Plasma PLP	[7]
		Women	1.84 ± 0.60	1.30 - 1.50			
202 non-pregnant Metro Vancouver women (19 - 35y)	Dietary recall	High household income	1.50 ± 0.47	1.90	1.5% plasma PLP < 20 nmol/L; 12.4% < 30 nmol/L; lower prevalence of deficiency of vitamin B6 deficiency among high income	Plasma PLP	[20]
		Low household income	1.40 ± 0.42				

mg (lactating women) depending on age, gender and health status. Some groups may have a higher risk for vitamin B6 deficiency because of a higher requirement. For example, the high B6 deficiency among nursing home residence may be a combined result of poor food intake and higher requirement [19,21]. Low vitamin intake in elderly increased the risk for frailty [22]. Among different groups, the prevalence of low vitamin B6 intakes were in general higher among women as compared to men [13-15] as shown in Table 1. A recent study in US found lower B6 intake in women compared to men but the use of B6 supplement led to sufficient total vitamin B6 intake in both gender groups [23].

Different populations with similar mean vitamin B6 intake do not always have the same prevalence of vitamin B6 deficiency. For example, despite similar B6 intake, B6 deficiency rate was only 1.5% among pregnant Vancouver women [20] yet 15.7% Korean adults showed deficiency [7]. The women in Metro Vancouver women study in general had higher socioeconomic status [20]. B6 deficiency reached 11% among Puerto Rican adults although the mean intake was higher than their requirement [18]. It is possible that in some populations, such as Puerto Ricans, there were a wider range of B6 intake and thus the mean intake cannot reflect the population B6 status. It is also possible that the bioavailability of vitamin B6 depends on the food type as discussed below. Other factors may also change B6 metabolism. This will explain why the correlation between B6 intake and B6 status is not always strong [20].

B6 availability depends on the food type: plant versus animal source

All forms of B6 are found in the food but their bioavailability varies. Plant foods have mostly the structure analogs of PN (the most stable form of B6) [7]. Glycosylated forms of PN found in some plant foods are poorly available for functional phosphorylation [24-26]. Also, dietary fiber in the plant causes incomplete digestion, which further reduce the bioavailability of PN [24]. The pre-cecal digestibility of vitamin B6 from plant products is on the average 10% lower than that of animal products and B6 in brown rice is only 16% digestible [27]. In contrast, animal products have mostly bioavailable PL, PM and their phosphorylated forms. Sirloin steak, salmon, and the light meat of chicken are rich sources of bioavailable B6 [26]. Thus, similar amount of total B6 intake may lead to different B6 status because of the difference in the bioavailability. Few studies considered the bioavailability of vitamin B6 from different food sources. PN found in the supplement or fortification improves vitamin B6 status [20] but the information on supplement usage or food B6 fortification is not always available.

A loss of vitamin B6 during the food storage and processing

The effect of cooking method on B6 stability also should be considered [26,27]. Most vitamins will suffer from some loss during storage and cooking based on the exposed temperature, sunlight, PH, moisture, oxygen and size of portions [28,29]. Thermal degradation of vitamin B6 increases as pH rises. Aldehyde group in PL and PLP can react with the epsilon-amino group of protein-bound lysine [24,30,31]. Because of this Schiff base reaction, the stability of the vitamin during processing of plant products, which contain predominantly PN, may be higher than that of vitamin B6 in animal products, which contain mainly PLP and PMP. Vitamin B6 is water-soluble and thus is at a higher risk of losing in liquid food. The loss of vitamins from vegetable is mainly through escaping into the cooking liquid [29]. In dehydrated food systems at 180 °C for 25 minutes, the loss of 50 - 70% of PN, PM and PLP added in experimental fortification was also observed [31]. Storage will also lead to the loss of vitamin B6. Storage at higher temperature or longer duration will increase the extent of loss [32-34]. The vitamin B6 content of baked cod has been reported to decline by 20% after 3 days of cold storage [29,35]. Large losses, ranging from 20 to 70%, can happen to both vegetables and animal products even in frozen foods [29,36].

Effect of exercise and weight control

Several population studies listed in Table 1 found women at a higher risk for low B6 intake and low plasma PLP level [13,16,18]. Compared to sedentary women, many female athletes consumed more energy. As a result, they had higher B6 intake that reduced the chance of B6 deficiency [2]. Nevertheless, low B6 intake was found in young women participating in sports where weight restriction was encouraged, and thus total energy intake was low [37,38]. Low total energy and B6 intake also happened in men intending to lose weight during sport training [39]. Gastric bypass surgery for morbid obesity was linked to general vitamin deficiency including 17.6% B6 deficiency at 2-year after the surgery in an earlier study [40]. However, a recent study showed that at a year after the surgery when diabetic, hypertension and hypercholesterolemia conditions were mostly eliminated, B6 status also improved [41]. The different post-surgery B6 outcome may be due to an improvement in the surgical procedures in the last decade as well as a wider use of vitamin supplement.

Table 2: Summary of conditions that increase the risk of vitamin B6 deficiency (plasma PLP < 20 nmol/L).

Factor	Subjects	Intake measurement	Vit B6 intake (mg/d)	Vit B6 status measurement	Plasma PLP (nmol/L)	Conclusion	Ref
Type 2 diabetes	22 patients (36 - 79y)	Dietary record	22 ± 6 µg/g protein/d	Plasma PLP; Urinary 4-PA	10.5 - 118.3	Increased renal clearance; lower intake	[42]
	20 control (19 - 23y)		31 ± 3 µg/g protein/d		52.7 - 113.3		
Renal transplantation	687 stable recipients (53 ± 13 y)	Dietary recall	1.77 ± 0.49	Plasma PLP	30% deficiency mean: 29.00	Diabetes; higher utilization of PLP due to inflammation	[43]
	357 control (54 ± 11y)		1.85 ± 0.56		11% deficiency mean: 41.00		
High-flux haemo-dialysis	14 patients (59 ± 5y)	3-day dietary record	4-wk 60 mg B6/d treatment	Plasma PLP	Prior to treatment: 5.9 ± 0.8 (100% deficiency)	Dialysis depleted B6; more utilization of PLP	[44]
					After treatment: 29.7 ± 5.3		
Chronic peritoneal dialysis	11 patients (26 - 70y)	3-day dietary record	First 4 weeks 1.3 ± 0.2	Plasma PLP	Prior to treatment 16 ± 3 (100% deficiency)	Inadequate intake; dialysis depleted B6	[45]
			16-wk, 5-10 mg/d supplement		After treatment: 52 ± 7		
Smoking	159 now (19 - 73y)	N/A	Normal Western-style diet	Plasma PLP, PL	15.4 ± 6.2	Higher utilization of PLP	[46]
	59 past (22 - 71y)				19.9 ± 7.9		
	68 control (18 - 64y)				18.9 ± 6.7		
Intensive care unit under nutritional support	46 patients (23 - 85y)	Medical record	D1 9.3 ± 16.4	Plasma PLP, PL, urinary 4-PA; erythrocyte alanine and aspartate amino transaminase activity	42.7 ± 14.5	Supplement can maintain good B6 status	[47]
			D14 17.5 ± 19.6		34.6 ± 14.8		
Inflammation	714 subjects (mean 76y)	Dietary recall	2.26 - 2.55	Plasma PLP	CRP < 6 mg/L: 52.6-59.2	Higher utilization of PLP in inflammation	[48]
			1.62 - 2.67		CRP ≥ 6 mg/L 29.2 - 45.8		
Cancers	963 patients (46 - 74 y)	N/A	N/A	Baseline plasma PLP, PL and PA before the study	32.9 - 75.6 (mean: 47.1)	Increased catabolism; higher utilization of PLP	[10]
	5576 controls (46 - 74y)				36.2 - 75.0 (mean:50.6)		
Colorectal cancer	613 patients (40 - 68y)	Dietary recall	1.5-2.5 (food); 1.5-2.8 (total)	Plasma PLP, PL, PA	17.5 - 99.9 (mean:35.9)	Increased catabolism; higher utilization of PLP	[6,49]
	1190 controls (40 - 68y)				19.0 - 107.1 (mean:38.20)		
Rheumatoid arthritis	33 patients (54 ± 12y)	Dietary recall	1.7 ± 0.9	Plasma PLP, urinary 4-PA, PLP functional assessments	19.5 - 31.1 (mean:24.7)	Increased phosphatase; lower plasma albumin	[50,51]
	17 controls (53 ± 14y)				35.3 - 60.3 (mean:46.2)		

Inflammation	743 each tertile (mean 61y)	Dietary recall	2.7 (0.9 - 4.5) 5.2 (3.4 - 6.9) 18.6 (16.8 - 20.3)	Plasma PLP	Mean 35 (CRP 3.1) Mean:69 (CRP 2.1) Mean:177 (CRP 1.8 mg/L)	Higher utilization of PLP in inflammation	[52]
Adults underwent coronary angiography (45-78y)	1313 B6 treatment T 664 placebos	N/A	4-wk B6 supplement (40 mg/d)	Ratios PA:PL, PA:(PL + PLP)	PA: PL = 0.26 PA:(PL + PLP) = 0.44 PA: PL = 0.61 PA:(PL + PLP) = 0.75	Increased catabolism; higher utilization of PLP in inflammation	[3,53]

Diseases and Inflammation

Data supporting links between various diseases and B6 deficiency have been compiled into Table 2.

Although lower B6 intake could increase the chance of B6 deficiency, other factors such as inflammation likely also influence B6 status. A study simultaneously measuring B6 intake, plasma PLP and inflammatory marker C-reactive protein (CRP) found a gradually higher plasma PLP with gradually higher B6 intake [52]. Interestingly, the highest tertile in B6 intake also had the lowest CRP level [52,54]. An older study found lower mean plasma PLP level among current smokers compared to that of past smokers and non-smokers [46]. All three groups in the study consumed normal western-style diet and sadly all had mean plasma PLP below 20 nmol/L, the cutoff for B6 deficiency.

Disease-specific pathological changes may also have significant effects on the plasma PLP levels. Excessive renal loss of B6 is expected in diabetic and dialysis patients. Indeed, vitamin B6 deficiency is common among these patients [42-45]. Two small trials both found that pharmacological doses of B6 were able to correct the deficiency [44,45].

Patients with inflammation due to various diseases and conditions were found to have lower vitamin B6 status compared to the control subjects. Because vitamin B6 is integrally involved in the white blood cell division and the production of cytokines and other polypeptide mediators during the inflammatory response [1,48,52], the intracellular retention of the active form of B6 as PLP is increased during systemic inflammation [55]. This can lead to a decrease in the plasma PLP pool. More irreversible degradation of PLP to PA can also lead to lower B6 status [3]. Alkaline phosphatase is a key enzyme in the degradation of PLP. Smokers had elevated heat-stable alkaline phosphatase isoenzyme that may result in an increased hydrolysis of PLP [18,46]. Elevated level alkaline phosphatase was also observed during systemic inflammation [51].

Patients with higher plasma CRP levels tended to have lower PLP levels [48]. In population studies, increased catabolism of vitamin B6, as indicated by the higher ratio of PA:(PL+PLP), can be explained almost exclusively by the inflammatory markers CRP, and white blood cells [3,6,9]. Because inflammation is accompanied by oxidative and aldehyde stress, several aldehyde-degrading enzymes including aldehyde oxidase and aldehyde hydrogenase are also upregulated and may promote the oxidation of PL to PA [44,45]. The deleterious effect of inflammation on B6 can be overcome by supplementation. Pharmacological doses of B6 improved the B6 status of adults after coronary angiography [53] and prevented B6 deficiency among patients in the intensive care unit [47].

Inflammation and vitamin C

In our examination of literature on inflammation, a link between inflammation and low vitamin C status was also noticed [56-62]. This link may also have impacted on the vitamin C status in US. Vitamin C intake in US is close to or exceeds the requirement in all age groups based on NHANES [63]. Yet 6% of the population in the same 2012 CDC report showed vitamin C deficiency when plasma ascorbic acid levels were analyzed. Vitamin B6 and C are the top 2 most deficient water-soluble vitamins in the CDC report.

Conclusions

Vitamin B6 coenzyme has a wide range of functional importance. Lower intake of vitamin B6 can contribute to B6 deficiency among vulnerable populations such as elderly and individuals with restricted energy intake or systemic inflammation. Although there is no sufficient information, vegetarians could also have an increased risk of deficiency because of the lower B6 bioavailability from plant sources. Renal diseases and elevated systemic inflammatory responses also changed B6 metabolism and increase the need of vitamin B6. Inflammation may have also increased vitamin C deficiency in US.

B6 supplementation appears to be effective in alleviating B6 deficiency although pharmacological doses may be needed in some cases. The use of vitamin C supplement is also known to increase plasma ascorbic acid level [64]. However, vitamin B6 and vitamin C are known to show toxicity upon prolonged high-level supplementation and both have Upper Levels established. Despite the possible link between inflammation and their deficiencies, high-level supplementation of these two water-soluble vitamins should only be considered under medical supervision.

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DOI: 10.36959/487/282