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LEADING ARTICLE

Vitamin B6 in Elite Athletes: Potential Implications of High Intakes

Thomas Valente van Keulen[1,2] · Nathan A. Lewis[2,3] · Charles R. Pedlar[1,2,4]

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Abstract
Vitamin B6 plays a role in over 100 enzymatic reactions, and it is purported that athletes have higher requirements compared with the general population. Deficiency, while rare, may lead to adverse symptoms if severe or prolonged. Conversely, excessive intake may increase the risk of toxicity. This article discusses the potential implications of high vitamin B6 exposure in athletes and includes illustrative observational data on plasma pyridoxal 5′-phosphate (PLP) from routine biomarker monitoring in elite athletes. Observation-level deficiencies (<30 nmol/L; 5.2%) and raised (>125 nmol/L; 38.7%) PLP measurements ($n = 654$) in elite athletes ($N = 396$) participating in routine biomarker screening, alongside implications of possible intakes above athletes' requirements are discussed. Athletes' use of nutritional supplements, sports beverages, or even intravenous nutrition, which contain highly bioavailable doses of vitamin B6, are a plausible contributor to the observed high PLP concentrations. Chronic total vitamin B6 intake above 21 mg/day, particularly with low protein intake, may increase toxicity risk.

Key Points

Exposure to vitamin B6 should be considered in the elite sport environment.

Elevated PLP reflects high overall vitamin B6 exposure but does not indicate toxicity, as clinical symptoms are primarily associated with chronic pyridoxine intake rather than circulating PLP.

A notable proportion of elite athletes and observations may display (sustained) supraphysiological fasting PLP concentrations, exceeding established laboratory reference ranges and recommended upper limits.

These findings suggest that routine monitoring may help identify athletes with unexpectedly high vitamin B6 exposure, given the widespread use of supplements and fortified products in high-performance sport.

✉ Charles R. Pedlar
charles.pedlar@stmarys.ac.uk

1 Faculty of Sport, Technology and Health Sciences, St Mary's University, Twickenham, UK

2 Orreco, Business Innovation Unit, National University of Ireland, Galway, Ireland

3 United Kingdom Sports Institute, Sports Training Village, University of Bath, Bath, UK

4 Institute of Sport, Exercise and Health, University College London, London, UK

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1 Background

Vitamin B6 comprises several interconvertible vitamers: pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM), and their phosphate forms: pyridoxine 5′-phosphate (PNP), pyridoxal 5′-phosphate (PLP), and pyridoxamine 5′-phosphate (PMP). PN is typically consumed in supplemental form, whereas PLP, the main bioactive form of vitamin B6, is a cofactor in metabolic pathways involving amino acid, oxoacid, or amine substrates. In humans, over 100 B6-dependent enzymatic reactions have been described [1, 2], contributing to a variety of essential physiological functions [3]. Vitamin B6 is found in a variety of animal and plant foods and can generally be consumed in amounts sufficient to meet requirements when energy needs are met. In high-income countries like the US [3, 4], UK [5] and Nordic-Baltic countries [6], major dietary sources include fortified cereals, meat, dairy products, vegetables and potatoes.

1.1 Vitamin B6 Bioavailability

The absorption of PN from supplements in the form of PN-hydrochloride (PNHCl), the most common form in food supplements, is almost complete (~95% is absorbed) [7]. In contrast, using plasma PLP and urinary 4′-pyridoxic acid (4-PA) as biomarkers of bioavailability, absorption from foods ranges from 36 to 92% [7, 8], depending on the gastric pH, vitamer composition, food matrix, and processing [7–9]. Overall, about 75% of vitamin B6 from a mixed diet is bioavailable [3, 7, 8]. Using PNHCl as a reference, 1 mg

of vitamin B6 from food is equivalent to 0.8 mg from food supplements [7]. Other supplemental forms show similar bioavailability [10].

1.2 Recommended Intake

In the US, the recommended dietary allowance (RDA) for men aged 14–50 years and women aged 19–50 years is 1.3 mg/day, which is increased to 1.9 and 2.0 mg/day during pregnancy and lactation, respectively [3], whereas in the UK the recommended nutrient intake (RNI) is 1.4 mg and 1.2 mg for men and women aged 19–64 years, respectively [11]. The maximum daily dose unlikely to cause adverse side effects in the general population, the tolerable upper intake level (UL), has been set at 100 mg for adults aged 19 years and older in the US [3, 12]. However, case reports of neuropathy at supplemental intakes below earlier ULs, the absence of a clear *lowest-observed-adverse-effect level*, and large inter-individual differences in both dose–response and time to onset have led to an updated UL of 12 mg/day set by the European Food Safety Agency (EFSA) [13], lower than the 25-mg/day limit set previously in 2000 by the Scientific Committee on Food [14].

1.3 Risk of Deficiency

Certain conditions exacerbate the risk of developing a deficiency by interfering with the absorption of vitamin B6. These include alcoholism, kidney disease, autoimmune intestinal disorders like coeliac disease, ulcerative colitis, Crohn's disease, and autoimmune inflammatory disorders (e.g., rheumatoid arthritis) [3, 12]. Vitamin B6 deficiency is rare in healthy populations (3–11% <20 nmol·L^{-1} despite adequate intakes in ≥99% of the UK population [11]), with reports scarcely found in the literature. Vitamin B6 deficiency more commonly occurs when the status of other B vitamins, particularly vitamin B12 and folate (vitamin B9), is also poor. Mild deficiencies may be asymptomatic, but more severe or prolonged deficiencies can manifest symptoms such as microcytic anaemia, skin conditions, depression, confusion, and lowered immunity [3, 12]. On the other hand, excessive vitamin B6 intake may result in toxicity. Symptoms of toxicity and related neuropathy include pain, paraesthesia in the extremities, ataxia, and nausea, which seem to subside when supplementation is discontinued [15–17].

1.4 Vitamin B6 Requirements in Athletes

Based on the current literature, active or athletic populations may require 1.5–2.5 times the current RDA (~2.0–3.0 mg/day) due to increased vitamin B6 turnover, metabolism, and nutrient losses [1, 18–20]. For instance, a 1994 study by Rokitzki and colleagues showed that marathon runners lost about 1 mg (~70–80% RNI) of vitamin B6 during a marathon race (26.2 mi or 42.2 km) by measuring the excretion of a vitamin B6 metabolite, 4-PA [21]. It is widely accepted that a varied diet is sufficient to satisfy the nutritional needs of athletes if energy intake is adequate [22].

Adequate concentrations of plasma PLP are set at a minimum threshold of 20–30 nmol/L [3, 7, 23]. Recently, assessments of vitamin B6 status using ratios between substrate–product pairs suggest that vitamin B6 becomes a rate-limiting factor for the metabolic flux across the kynurenine pathway when plasma PLP concentrations drop below 100 nmol/L [24, 25]. Specifically, studies investigating changes in plasma metabolites suggest that PLP concentrations below 30–50 nmol/L may be considered inadequate, given biochemical perturbations [26–28].

1.5 Vitamin B6 Regulation

Fasting plasma PLP concentration is a regulated marker of body stores, not a simple reflection of recent intake. Metabolic balance studies show that PLP clearance (4-PA) declines more rapidly than fasting PLP concentration, suggesting that plasma PLP tracks hepatic stores more closely than intake, whereas urinary 4-PA is more sensitive to short-term intake [29, 30]. Equally, with supplemental PN, systemic B6 clearance may be stunted, as shown by Lui and colleagues [29]. In this context, elevated fasting PLP concentration indicates sustained high exposure and enlarged body pools, even though plasma PLP is not itself a validated toxicity threshold.

1.6 Bioaccumulation and B6-Related Neurotoxicity

Despite tight regulation, elimination studies suggest that rate constants of elimination indicate a tendency for B6-vitamers to accumulate when PN doses are given repeatedly [31]. Specifically, plasma PN concentrations rise, and metabolites increase with repeated dosing overlapping peaks due to incomplete inter-dose clearance.

Using 173 reported cases of vitamin B6-related neuropathy cases reported to the Netherlands Pharmacovigilance Centre Lareb through January 2019, Vrolijk and colleagues have shown that of all reports, 96 patients (55.5%) used vitamin B6 supplements, without co-medication [32]. Interestingly, only 3.5% (6 out of 173) of these cases were caused by PLP supplementation, whereas 96.5% were due to PN supplementation [32]. Indeed, symptoms of toxicity are reported to be easily reversed by ceasing supplementation as the vitamin is excreted [15, 33–35]. Neurotoxicity is

purported to be caused by PN accumulation, which occurs solely with supplemental PN intake [32, 36–38].

Tissue-specific PLP depletion resulting from PN supplementation, where disrupted GABA neurotransmission may trigger excitotoxic neurodegeneration, has been proposed as a mechanism underlying the observed neuropathy [36]. Consistent with the reported cases of B6 toxicity, PN has shown to have poor blood–brain barrier permeability in mechanistic studies [39, 40], confining these effects to the peripheries. Detailed discussion of these mechanistic aspects is beyond the scope of this leading article. For detailed discussions of these mechanisms and potential effects, readers are referred to reviews by Salvo et al. [41], Hadtstein and Vrolijk [36], Sun et al. [42], and EFSA [7].

2 PLP Concentrations in Elite Athletes

Recently, we have observed several athletes presenting with plasma PLP concentrations above recommended ranges. This prompted the present discussion of vitamin B6 exposure and requirements in athletes. To contextualise this concern, we analysed 654 observations from 396 elite athletes, categorising measurements into deficiency (PLP <30 nmol/L), insufficiency (PLP ≥30 to <50 nmol/L), sufficiency (PLP 50–125 nmol/L), or excess (PLP >125 nmol/L). The observations are illustrated in Fig. 1. Methodological details are provided in the Electronic Supplementary Material (ESM).

Overall, we found that PLP excess was common, occurring in 38.7% of observations and in 41.9% of athletes at least once, averaging 40.3% of excess measurements per athlete (see ESM, Table S2 and Table S3). Repeated sampling across seven seasons (2017–2024) suggested that elevated PLP was often sustained over time, whereas deficiency was uncommon and never persistent (ESM, Table S4). Athletes with repeated samples had higher median PLP (ESM, Table S1) and among these, 16% had all observations categorised as excess. These observations do not establish clinical harm, but they support the possibility that high intake may contribute to B6 excess, increasing the risk of potential, unknown side effects.

3 Literature Context

Our observations and those of others suggest athletes may consume vitamin B6 in amounts exceeding the RDA. For example, blood samples were collected from 48 elite and sub-elite Dutch athletes (29 male and 19 female) to assess nutritional status [43]. No athlete was below the lower reference limit set in the study (51 nmol/L). Unfortunately, the vitamer form assessed was not reported. However, 10% of male athletes exhibited whole blood plasma PLP exceeding 183 nmol/L [32, 33].

There is no defined threshold for toxicity. Defining a clear threshold that distinguishes normal from potentially unsafe circulating vitamin B6 concentration remains challenging due to differences in biomarkers analysed, levels of exposure to vitamin B6 and the type of vitamer ingested (e.g., PN vs PL), varying latency periods, and blood handling techniques (e.g., vitamer or blood fraction analysed: whole, serum, or plasma vitamin B6) as well as individual responses. For example, in a case study, one individual had vitamin B6-related nerve damage at circulating PLP concentrations of 80 nmol/L and one at 650 nmol/L PLP [33]. Toxicity to nerves is often shown to be related to

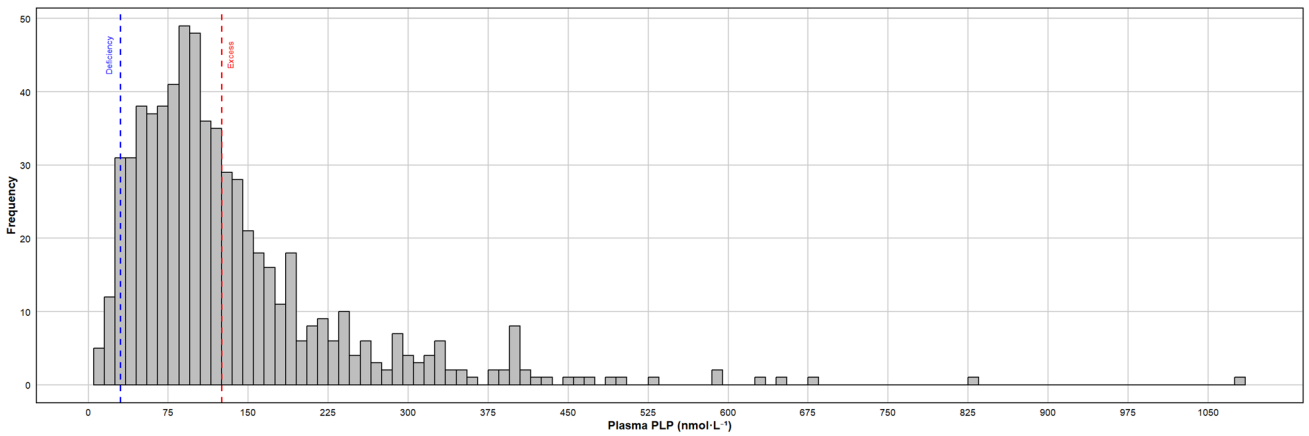

Fig. 1 Histogram of plasma pyridoxal 5-phosphate (PLP) concentrations across 654 observations from 396 elite athletes (17 females, 379 males). Each athlete contributed between 1 and 12 samples (median 1; IQR 1–2); observations are not independent. Bin width = 10 nmol/L with x-axis scaled in 25-nmol/L intervals. *Blue and red dashed lines* denote cut-offs for vitamin B6 deficiency (plasma PLP <30 nmol/L) and excess (plasma PLP >125 nmol/L), respectively

high (≥ 3 × the physiologically required concentration of 20–30 nmol/L) PLP concentrations, but this is variable. For instance, Vrolijk et al. observed B6-related toxicity in subjects with plasma PLP concentrations ranging from 88 to 5656 nmol/L [32]. The risk of neurotoxicity is likely exacerbated when vitamer-conversion pathways are saturated due to high supplemental intake [37], resulting in elevations in both PN and PLP concentrations, and when total vitamin B6 intake is ≥21 mg/day [32] or protein intake is low [38].

In the general population, side effects seem to arise from supplementation rather than from dietary intake via natural food sources. Because vitamin B6 is a water-soluble vitamin, its excretion is typically sufficient to prevent excess and toxicity, except in cases of prolonged, high-dose supplementation. Most of the available evidence in humans can be derived from case reports, suggesting that clinical neuropathy occurs at exposure levels between 100 and 6000 mg/day of vitamin B6 over variable latency periods ranging from 1 to 72 months [13]. However, case studies have reported neuropathy incidence in subjects taking supplemental PN at doses near or below 25 mg/day [44, 45], and as low as 0.5 mg/day [13].

Thus far, we have found no reports of vitamin B6-related adverse effects in athletes; however, the possibility of detrimental effects on health and performance remains and the risks should not be neglected. Interestingly, several case studies report vitamin B6 toxicity secondary to high intake of supplemental PN from consuming multivitamins [33, 34, 44], over-the-counter vitamin supplements [15, 35], with [33–35] or without [15] intake of energy drinks.

4 Supplementation

It has been reported that nutrient fortification and supplementation are more common in the United States than in Europe [46, 47]. When accounting for supplementation, 1–10% or 1–6% of Americans exceeded the UL for niacin and folate (B6 was not investigated), respectively [47]. American's consumption of supplements and energy beverages has risen in recent years [47–49]. About 28–36% of Americans use supplements containing vitamin B6 [12, 47] and up to 98% of athletes consume supplements [50–52]. Athletes are among the largest consumer groups of energy drinks [53, 54]. For instance, energy drinks were shown to be the most commonly consumed supplement among elite young British athletes [52] and varsity athletes at a Division I university [51]. While our data suggest that cases of excess PLP concentrations were relatively more common in Europe (53.8% vs 35.9%), the PLP concentrations within those with excess PLP were higher in the Americas (median concentration: 157.2 vs 195.3 nmol/L) (ESM, Table S5).

Jagim and colleagues [55] identified the top 75 commercially available energy drinks and energy shots from commercial retail websites (e.g., Amazon, Walmart, Kroger, Target). The relative prevalence and average contents (± SD) of the top ingredients were caffeine (100%; 174.4 ± 81.1 mg), vitamin B6 (72%; 366.9 ± 648.1% daily value [DV]), vitamin B3 (67%; 121.4 ± 69.9% DV), vitamin B12 (67%; 5244 ± 10,474% DV), vitamin B5 (37.3%; 113.6 ± 76.6% DV), and taurine (37.3%; undisclosed). B vitamins, including B6, are important in the production of energy from carbohydrates [56]. Because energy drinks often contain large amounts of sugar, these vitamins are added to purportedly aid the conversion of sugar to energy, acting as a selling point to consumers. An important and novel source of exposure to supraphysiological concentrations of vitamin B6 is the recent rise of intravenous nutrition use in team sports [57]. Apart from likely violation of anti-doping rules, this poorly regulated and poorly understood nutritional intervention poses a risk not only of megavitaminosis but also contamination.

5 Career Length and Latency Period

Professional athletes in leagues such as the National Basketball Association (NBA), National Football League (NFL), National Hockey League (NHL), and Major League Baseball (MLB) have careers averaging 66–98 months [58]. Compared with the typical latency period of 1–72 months for symptoms of vitamin B6 toxicity to appear [13], the risk of cumulative exposure becomes more pronounced as an athlete's career progresses. To illustrate this plausible exposure risk, consider an athlete participating in seven training sessions and one match per week. If they consume one energy drink per training session and two per match (pre-match and half-time), their daily intake of vitamin B6 from energy drinks alone could average 8 mg/day, based on the values reported by Jagim et al. [55]. Over time, this supplemental intake may increase toxicity risk. This may be exemplified by a case of vitamin B6 neurotoxicity from multivitamin-derived PN intake of 6 mg/day over 18 months in a 73-year-old male [44]. When additional sources such as multivitamins, intravenous nutrition, and dietary intake are considered, athletes may plausibly approach or exceed the UL of 12 mg/day set by EFSA. Genetic variation in B6 metabolism (e.g., PNPO/PDXK) may modulate individual responses. While these data were not available in our cohort or other articles, our data suggest a non-trivial proportion with supraphysiological exposure where long-term risk—particularly if under chronic high supplemental intake and in susceptible individuals—remains uncertain.

6 Implications for Athletes and Practitioners

Many supplements, sports/energy drinks, and/or their combinations contain high amounts of vitamin B6, beyond the physiological requirements of healthy individuals. Athletes are consumers of these products and are thus at increased risk of hypervitaminosis, which may in some cases be inadvertently further exacerbated by multivitamin use and intravenous nutrition.

For athletes, vitamin B6-derived neuropathy, even at subclinical levels, could hypothetically impair technical and cognitive performance, increase injury susceptibility, and ultimately shorten career length if left unchecked. Given career longevity is closely linked to athletic success and earning potential [58], monitoring and managing vitamin B6 status may represent a valuable strategy to support long-term athlete performance and health. Toxicity from chronic elevated blood concentrations is plausible, with the potential to result in neuropathy.

We suggest that toxicity risk is highest when (i) PN is ingested, (ii) the total (from food and supplements) daily vitamin B6 dose is >21 mg, (iii) the diet is low in protein, and (iv) blood concentrations are chronically high (1–72 months' latency). Accordingly, monitoring vitamin B6 in athletic populations may help identify and address both deficiency and excessive exposure (see Fig. 1). Given the uncertainties around long-term exposure, cautious interpretation is warranted. Practitioners working closely with this population should be aware of the risks associated with supraphysiological vitamin B6 intakes. Attention should be given to supplemental intake from sources containing PN.

7 Conclusions

The observational data and wider literature context presented in this leading article suggest that while vitamin B6 deficiency is rare, high circulating concentrations are common and persist with time. Vitamin B6 bioaccumulates with chronic supplemental PN intake, but the long-term implications remain poorly characterised in the general population and have not been established in athletic populations.

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Declarations

Conflict of Interest All authors are consultants with Orreco, a sports bio-analytics company which provides biomarker analysis services for elite athletes.

Ethics Approval and Consent Ethics approval was provided by St Mary's University, Twickenham (SMU_ETHICS_2023-24_652). Athletes provided informed consent. All athletes included in the present study were engaged in regular blood biomarker screening and represented their club or country at the highest level (e.g., professional or elite level).

Availability of Data and Materials The relevant data used in longitudinal monitoring of elite athletes cannot be shared publicly because they contain potentially sensitive information and are protected under the EU General Data Protection Regulation. Anonymised data are available upon request for researchers who meet the criteria for access to confidential data.

Author Contributions All authors conceptualised the study. The primary researcher (TVvK) completed the literature review, data analyses and write-up. NL and CP coordinated the project, including data collection, and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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