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Problematic rise of vitamin B6 supplementation overuse and potential risk to bariatric surgery patients.

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Highlights :

- We observed a problematic increase in vitamin B6 overdoses in our patient population in the last 10 years.
- This is likely linked to the rise in bariatric surgeries, which require life-long follow up for deficiencies.
- While vitamin B6 deficiency is associated with growth retardation, high doses of pyridoxine can induce polyneuropathy, notably targeting motor neurons.

- While supplementation for at risk patients (including the elderly and bariatric surgery patient) is of paramount importance, our results demonstrate the importance of the source and composition of supplement, as the risk for vitamin B6 overdose needs to be taken into account
- The rise of overdoses is worrying and due to the ease with which these could be averted, we believe that the definition of clear guidelines for vitamin B6 supplementation is required.

Abstract

Background: Due to the increased prevalence of obesity in the world, bariatric surgeries are on the rise and necessitate life-long surveillance for deficiencies, hence the recommended vitamin supplementation in these patients. However, inadequate multivitamin supplementation may induce vitamin B6 overload.

Methods: We reviewed all the vitamin B6 dosages realized at university hospitals of Poitiers, Tours, Bordeaux and Limoges for the last 5 to 8 years. Analyses were performed by HPLC coupled with a fluorescence detector on whole blood samples. Results: During this time, there was an increase in the number of vitamin B6 dosages. While deficiencies were detected early on in Poitiers and Limoges, by 2020 there were negligible. However, during the same period the number of overdoses increased, reaching close to 40% of dosages in all centers. Conclusion: Pyridoxin overload is not possible through food-derived pyridoxin, hence combined with the fact that most vitamin supplements contain vitamin B6 it is likely that inadequate vitamin supplementation is the cause of the observed rise in overdoses. High doses of vitamin B6 can induce polyneuropathy, particularly targeting motor neurons, the rise of overdoses is thus worrying. In light of the possible risks, and the ease with which these could be averted (better formulation of supplements), the precaution principle requires the definition of clear guidelines for vitamin supplementation, especially in bariatric surgery patients.

Keywords: Vitamin B6; Overdose; Bariatric surgery; Neuropathy

1. Introduction

Vitamin B6 is a water-soluble vitamin with three major forms: pyridoxin (the form predominantly used in clinical treatment), pyridoxal and pyridoxamin as well as their phosphorylated derivatives [1]. It can be found in many types of food, however in fruits, vegetables and grains it exists only in its glycosylated form, which reduces bioavailability [2] the richest sources of vitamin B6 include fish, beef liver and other organ meats, potatoes and other starchy vegetables.

It plays a major role as coenzyme in different reactions within the metabolisms of lipids, hemes, nucleic acids, proteins or carbohydrates [1]. In the amino acid metabolism, vitamin B6 is involved in the synthesis of neurotransmitters which explains its important function in the nervous system [3]. Pyridoxin also plays a role in the immune and endocrine systems [4].

Vitamin B6 deficiency is associated with growth retardation, pellagra-like dermatitis and ataxia [4]. The most uncommon and severe symptom of low level of pyridoxin are related to the nervous system: convulsion, hyperirritability, depression... [3] Infants with convulsion resistant to anti-epilepsy drugs respond well to pyridoxin injections [5]. In the elderly, a long-term vitamin B deficiency is associated with the occurrence of dementia [6].

Paradoxically, high doses of pyridoxine can also induce polyneuropathy [7]. Different clinical studies [8–10] reported sensory neuropathy after chronic high dose pyridoxin intake and the authors observed that the symptoms regressed on withdrawal of vitamin supplements.

Nowadays, vitamin B6 is dosed in at-risk patients: individuals with impaired renal function, rheumatoid arthritis, malabsorption syndrome, or alcohol dependence are among those most likely to have vitamin B6 deficiency [2]. Therapeutic strategies against metabolic diseases, such as hyperthyroidism, can also include vitamin supplementation and monitoring [11].

The prevalence of obesity in the world continues to rise (600 million patients in 2015) and bariatric surgery is now proposed as a treatment for the most severe cases [12]. In France, the number of this procedures has increased twenty-fold in twenty years [12]. This surgical gesture is frequently associated with nutritional deficiencies [13], with increased risk in certain situations such as pregnancy, justifying a vitamin supplementation. However, while supplements provide vitamin B6, pyridoxin seems to be one of the few micronutrients for which no deficiency has been observed [14]. Indeed, vitamin B6 is not among the recommended vitamins to monitor and supplement after bariatric surgery (whether in the US [15] or in France [16]), however, it is omnipresent in multivitamin product, which use is recommended for the bariatric surgery patient, with one tablet for patients treated by laparoscopic adjustable gastric band and up to two tablets for biliopancreatic diversion with duodenal switch, Roux-en-Y gastric bypass or sleeve gastrectomy [15]. A survey of the most popular brands of multivitamin products (Table 1) reveals that they all contain at least the recommended daily allowance for vitamin b6, and sometimes reach three to nine times this amount. Taking into account the fact that patients already receive the minimal dose through regular nutrition (recommended daily intake: table 2), this implies that most, if not all, patients are exposed to a minimum of twice the daily allowance in vitamin B6. This does not take into account vitamin B6 intake from other over the counter care products.

Hence, an inadequate multivitamin supplementation after bariatric surgery may induce vitamin B6 overload.

We reviewed all the vitamin B6 dosages realized at university hospital of Poitiers during the last eight years to see the evolution of the demand. We also evaluated the number of patients overexposed and in deficiency.

2. Materials and Methods

2.1. Study population

We retrospectively collected all the vitamin B6 measurements realized in patients at the University Hospitals of Poitiers, Tours, Limoges and Bordeaux in a period ranging from the 1st January 2012 to the 31 December 2020. The samples send by external centers are also included in this study. In total 40 311 samples were included in this study.

2.2. Laboratory analysis

In all centers, analyses were performed with a Chromsystems kit for vitamin B6 dosage (REF: 52052, Chromsystems, Germany). The quantification of derivatized vitamin is realized using HPLC coupled to a fluorescence detector. The column and pre-column are provided with the kit. The wavelengths used are 320 nm (excitation) and 415 nm (detection). Integration was performed with the Empower Software. This analysis quantifies the PLP (the pyridoxal-5'-phosphate), the most active form of the vitamin B6.

3. Results

We reviewed 40 311 vitamin B6 dosages realized between 2012 and 2020 (Table 3). Women are more likely to require this analysis than the men (64% women and 36% men). The most represented age group is 41-60 years old.

Analysis of the date (Figure 1) revealed that:

-The number of vitamin B6 dosages has steadily increased, with higher speed in smaller hospitals (Poitiers and Limoges).

-In Poitiers and Limoges, during the first half of the analysis period, vitamins B6 deficiencies (<30 nmol/L) were more frequent than hypervitaminoses (>100 nmol/L).

-During the last half of the follow up, vitamins B6 deficiencies decreased while we observe an increase of vitamin B6 overdose. This was particularly obvious in small centers, however larger centers were also impacted.

To better investigate this issue, we divided overdosage in three categories: 101-200 nmol/L which represent a level inferior to twice the maximum safety level, 201-500 nmol/L highlighting more important overdosing from twice to five times the maximum safety level, and a superior to 500 nmol/L category which actually is superior to the linearity limit of the technique.

Until 2017, overdoses were uncommon and rarely over 500 nmol/L. From 2018 on, the number of hypervitaminoses increased. Most of them were between 101 to 200 nmol/L but there was an increase in patients in the 201-500 nmol/L category. Regarding the superior to 500 nmol/L patients, while they were negligible before 2017, there is also an important rise since 2018. Over all centers, vitamin B6 overdoses are detected between 30 to 40% of patients.

4. Discussion

In the last decade, the number of vitamin B6 dosage has very strongly increased. In parallel with those assays, the number of overdoses has increased whereas the number of deficiencies are now negligible. These observations suggest that a factor providing vitamin B6 (such as nutritional supplements consumption) is increasingly used.

The increase of vitamin B6 dosage could be correlated with the increase of bariatric surgery. Indeed, even if there is no data on pyridoxin deficiency associated with bariatric surgery [14], vitamin B6 assay is often asked by clinicians in the preoperation examination or in the follow-up of the operation. Indeed, patients undergoing bariatric surgery have a severely altered diet, which renders them particularly sensitive to macro- and micro-nutrient deficiencies [17,18]. Unfortunately, monitoring of

these patients for such issues appears to decrease [19], which enhances the risk for deficiencies [20] leading professional societies to not only recommend multivitamin and micronutrient supplementation, but also close monitoring of patient adherence over time [21]. It is thus of paramount importance that this at-risk population are rigorously followed, with proper supplementation for macro- and micro-nutrient. Our results demonstrate the importance of the source and composition of supplement, as the risk for vitamin B6 overdose needs to be taken into account.

One of the other indications for the dosage of vitamin B6 is the survey of the nutritional supplements consumption. According to a French study [22], the consumption of the vitamin supplements has been multiplied by 2 between 2006 and 2014. In 2015, 22% of adults and 14% of children in France used vitamin supplements [22]. This increase in vitamin supplement consumption could also explain the inversion between the number of vitamin B6 deficiencies and overdoses. In two of our four centers until 2017, there were more deficiencies in vitamin B6 than overdoses. Nowadays, there is almost no deficiencies whereas the overdoses increase each year. Pyridoxin overload is not possible with the pyridoxin from food [23]. However, an overdose is possible with inadequate intake of vitamin B6 supplements.

This trend of high blood concentrations of vitamin B6 has been observed and known for a few years in the clinic, however lack of information on its impact has kept concerns at a minimum. However, a study from Vrolijk *et al.* shows that pyridoxin can induce cell death in neurons, and pyridoxal-5'-phosphate, the most active form of vitamin B6, can prevent pyridoxin induced cell death by a competitive mechanism [1]. Physiologically, pyridoxin is converted into pyridoxal-phosphate by the pyridoxal kinase and the pyridoxin phosphate oxidase. But at high doses (for example: vitamin B6 over supplementation), pyridoxin saturates these enzymes and it accumulates, generating neurotoxicity. Several studies reported sensorimotor neuropathy after intake of high dosage neuropathy

[7,8,10,14,24]. A recent study also highlighted an increased risk of lung cancer for men using vitamin b6 supplementation, albeit not when in the case of multivitamin supplementation [25].

Nowadays, most people who use food supplements are elderly people, pregnant women and people who had bariatric surgery. While it is difficult to gauge the effect of overdose over time, with only cellular and animal studies to rely on, we feel that there should be evaluations of the possible consequences of high vitamin B6 dosage in these such vulnerable populations. Indeed, inadequate supplementation in pyridoxin could participate in the development of sensorimotor neuropathy in these populations.

While guidelines exist regarding vitamin B6 deficiencies, no clear guidelines exist regarding high doses. The Food and Nutrition Board communicated tolerable upper intake levels (table 2) [23] but they remain untranslated into plasma concentrations and are not based on solid evidence.

5. Conclusions

In light of the possible risks, and the ease with which these could be averted, through monitoring of circulating vitamin B6 level and adjustment of supplementation, the precaution principle requires the definition of clear guidelines for vitamin B6 supplementation, and vitamin supplement composition, especially for at-risk patients.

Author Contributions: Conceptualization, VB, NB, TH and RT; methodology, VB and RT; validation, VB, NB, TH and RT; formal analysis, VB; investigation, VB and RT; data curation, VB, SP and PD; writing—original draft preparation, VB, SP and PD; writing—review and editing, NB, TH and RT; visualization, VB and RT; supervision, RT; funding acquisition, TH. All authors have read and agreed to the published version of the manuscript.”

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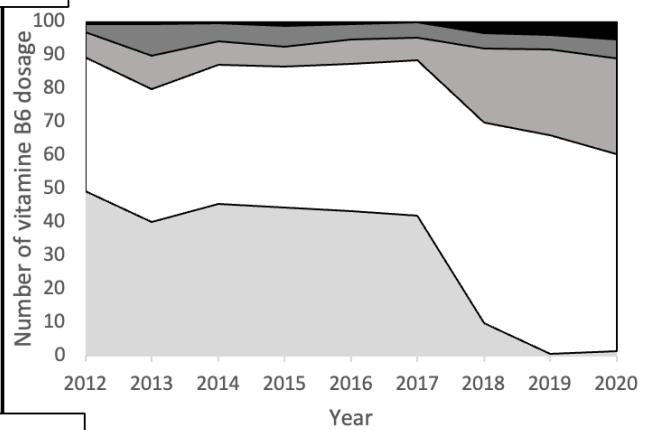
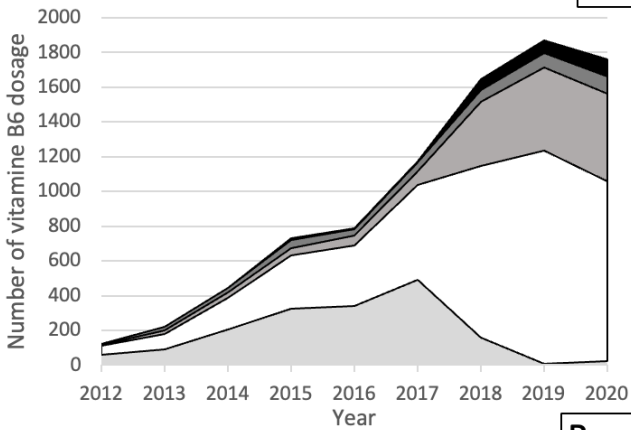
Data Availability Statement: Data is available upon request to the corresponding authors.

Figure legends:

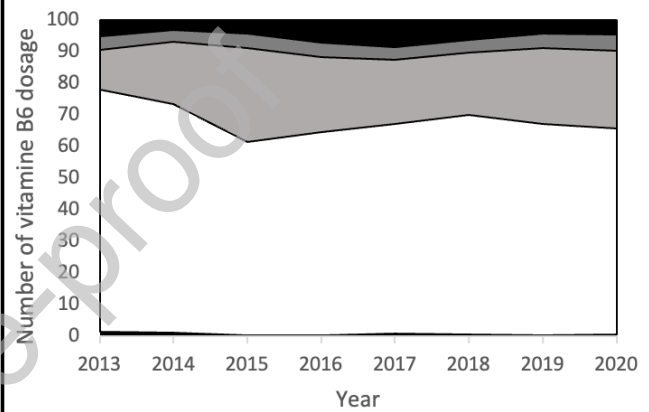
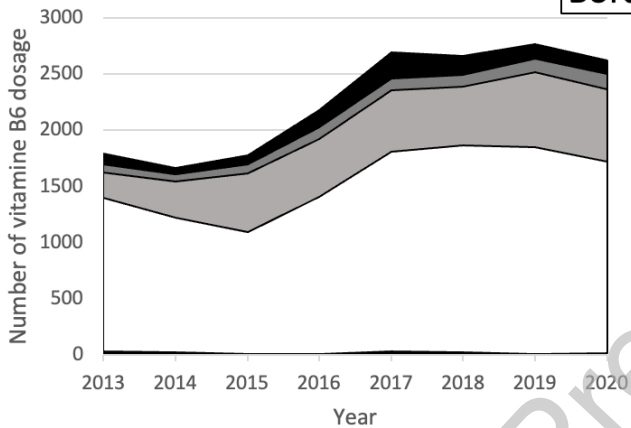
Figure 1. Number and level of vitamins B6 dosage from 2012 to 2020 in the different centers

To investigate the circulating levels of vitamin B6 in patients included in this study, they are represented in raw numbers (left) as well as percentage (right). Levels were divided into 5 groups: Deficiency (0-29 nmol/L), Normal (30-100 nmol/L), medium overdose (101-200 nmol/L), high overdose (201-500 nmol/L), very high overdose (> 500 nmol/L).

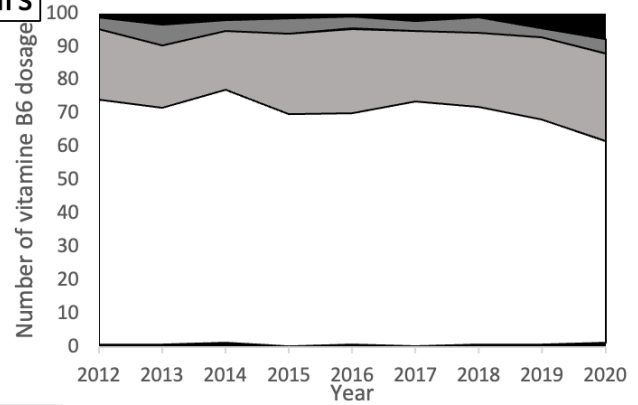
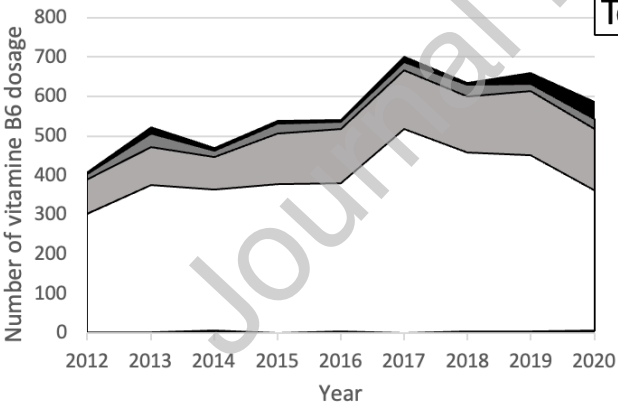
Poitiers



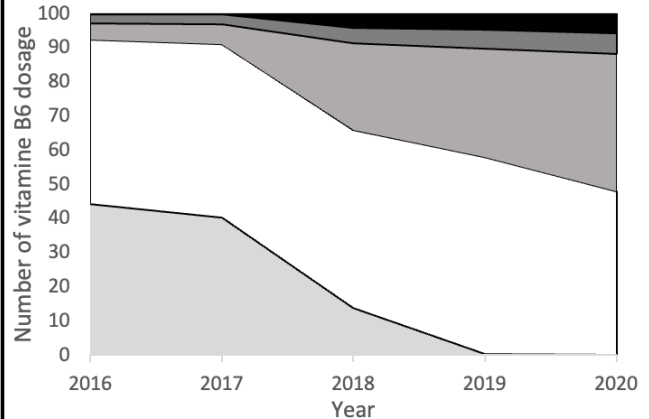
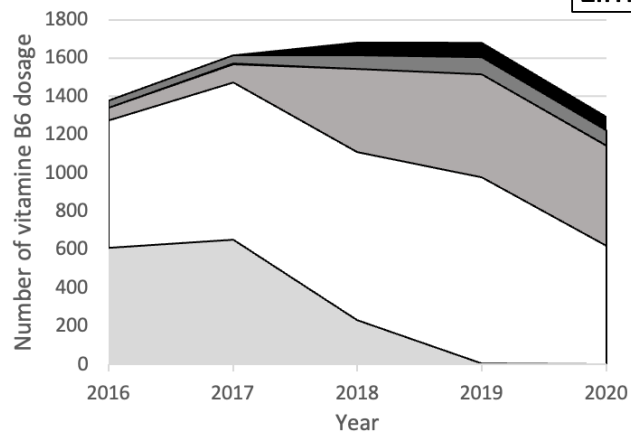
Bordeaux



Tours



Limoges



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Table 1. Amount of vitamin B6 in popular brands of multivitamins

Product Name	Vitamin B6 (mg) per tablet	% RDA
Centrum Silver	6	429%
Alpha Men Multivitamin	12,6	900%
WLS Optimum	1,5	107%
Vitafusion	1,7	121%
ForcaPil	2	143%
Nutri&Co	2	143%
Les Miraculeux Boost Immédiat	2,7	193%
Effinov Lifinov	1,61	115%

BOIRON BION 3	2	143%
Fitforme WLS Optimum	1,5	107%

Brands were chosen according to popularity (number of sales by country or overall). RDA: recommended daily allowance, based on 1,4 mg / day.

Table 2. Recommended daily allowance and Tolerable upper intake levels in vitamin B6

Age	Recommended daily allowance				Tolerable upper intake levels			
	Male	Female	Pregnancy	Lactation	Male	Female	Pregnancy	Lactation
Birth to 6 months	0.1	0.1			Not possible to establish	Not possible to establish		
7–12 months	0.3	0.3			Not possible to establish	Not possible to establish		
1–3 years	0.5	0.5			30	30		
4–8 years	0.6	0.6			40	40		
9–13 years	1.0	1.0			60	60		
14–18 years	1.3	1.2	1.9	2.0	80	80	80	80
19–50 years	1.3	1.3	1.9	2.0	100	100	100	100
51+ years	1.7	1.5			100	100		

From [18], values are in mg.

Table 3. Distribution of vitamin B6 dosages according to age

Age in years					
<21	21-40	41-60	61-80	>81	Total
3249	9561	14841	9916	2744	40311

Patients were retrospectively included from 2012. All patients for which vitamin B6 blood measurement was demanded were included. The gender balance was 64% women and 36% men.