REVIEW

A Systematic Review Evaluating the Effect of Vitamin B6 on Semen Quality

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Purpose: This review systematically discusses and summarizes the effect of vitamin B6 on semen quality.

Material and Method: To achieve this contribution, we searched the PubMed, Scopus, and Web of Science databases for English language papers from 1984 through 2017 using the key words "sperm" versus "Vitamin B6", "pyridoxine", and "pyridoxal". Also, the references from selected published papers were included, only if relevant.

Result: To date, as revealed by rodent studies, high doses of vitamin B6 impair semen quality and sperm parameters. While in humans, it is suggested, but not yet directly approved, that seminal vitamin B6 levels may alter sperm quality (i.e., sperm quantity and quality), and that vitamin B6 deficiency may trigger the chemical toxicity to sperm (i.e., hyperhomocysteinemia, oxidative injury).

Conclusion: The adverse effect of vitamin B6, when used at high doses, has been revealed in experimental animals, but not yet directly approved in humans. Consequently, in vitro studies on human ejaculate as well as clinical studies that investigate the direct effect of vitamin B6 on semen quality seem very significant.

Keywords: pyridoxine; pyridoxal-5' phosphate; semen quality, sperm; vitamin B6.

INTRODUCTION

Vitamin B6 is a water-soluble vitamin and a member in the vitamin B group essential for normal growth and development[1,2]. It is present in a variety of foods with a high content in walnuts, meat products, soybeans, and chicken breasts[3,4].

The important known role of vitamin B6 in the developing human body is in metabolism, particularly of the neurotransmitters[1,5]. The common biologically active form of vitamin B6 is pyridoxal-5' phosphate, which is a coenzyme for more than 100 known enzymatic reactions, mainly those of amino acid and carbohydrate metabolism[1,6].

In point of fact, the important biochemical function of vitamin B6 in the human body suggests it has a role in sperm maturation and sperm parameters. Therefore, several studies have linked vitamin B6 with semen quality; this effect, however, has yet to be summarized and collectively discussed. This review systematically discusses and summarizes the up-to-date evaluation of the effect of vitamin B6 on semen quality.

MATERIAL AND METHODS

Information source

To accomplish this contribution, we searched the PubMed, Scopus, and Web of Science for English language articles from 1984 through 2017.

Search strategy

We performed an inclusive electronic search until June 2017 using the key words "sperm" versus "Vitamin B6", "pyridoxine", and "pyridoxal" in the above databases. Additionally, certain relevant references were included to support the empirical results and the mechanistic discussion.

Eligibility criteria

This review included animal and human studies. The abstracts or full texts of all articles from the systematic search were extracted and carefully studied. Each included article was carefully assessed based on its full text that directly or indirectly introduces the effect of vitamin B6 on semen quality. The articles that do not present the effect of vitamin B6 on semen quality were excluded (not related). In addition, reviews and non-English abstracts/full texts were also excluded.

RESULTS

The literature searches retrieved a total of 23 potential records (**Figure 1**). After abstract and full text reading, a total of 12 articles met our inclusion criteria (**Table** 1). The majority of the included research studies that have directly linked vitamin B6 with semen quality were nonclinical (i.e., rodent studies) (8 studies). The human studies in this context were only four articles. We could not conduct meta-analysis in this systematic review because of the heterogeneity of the data.

Summary of selected study and design

The in vivo system studies were conducted in Japan (6 studies), United Kingdom (1 study), and Switzerland (1 study) (**Table 1**). While the human studies were conducted in Netherlands (2 studies), Canada (1 study), and France (1 study). Seven studies from the in vivo system ones were conducted on rats, and only one study was conducted on mice.

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Table 1. Summary of the studies that investigated (directly and indirectly) the effect of vitamin B6 or its derivatives on semen quality.

Ref.	Location	Affecter	Population	Outcome
(7)	Japan	Pyridoxine hydrochloride	Wistar male rats	-Lower weights of the epididymis, testis, prostate gland, and seminal vesicle. -Decreased mature spermatid count.
(8)	United Kingdom	Pyridoxal 5'-phosphate	Male mouse	-Decreased testicular lactate dehydrogenase
(9)	Japan	Pyridoxine	Wistar male rats	-Reduced spermatogenesis -Decrease in reproductive organ weights -Increase in testicular markers: beta-glucuronidase activity, cytochrome P-450 content and cytochrome b5 content
(11)	Japan	Vitamin B6	Wistar male rats	-Decreased sperm count -Decreased sperm motility - Phagocytosis of mature spermatids by Sertoli cells
(10)	Japan	Pyridoxine	Wistar male rats	-Alteration in testicular cells -Delay in spermiation
(12)	Japan	Pyridoxine	Male Jcl: SD rats	-Decreased sperm motility -Decrease in testicular proteins -Histopathological alterations in the testes -Decrease in epididymis weight
(13)	Japan	Pyridoxine	SD-Slc male rats	-Sperm morphology alteration -Sperm physiology alteration
(14)	Switzerland	Pyridoxine	Male rats	-Sperm motility changes -Sperm morphology changes -Histopathological alterations in the testes
(15)	Netherlands	Pyridoxine	Men of couples undergoing in vitro fertilization or intracytoplasmic sperm injection treatment	-Change in semen volume
(16)	Canada	Pyridoxal-5' phosphate	Humans	-Activation of seminal monoamine oxydase
(19)	France	Vitamin B6	Humans	-Altered spermatogenesis
(21)	Netherlands	Vitamin B6	Humans	-Change in seminal Homocysteine

Primary outcomes

The primary outcomes of the included studies were sperm parameters (e.g., count, motility, morphology, and volume), histological changes in the testes and male reproductive organs, and certain seminal enzymes and biomolecules.

Effect of vitamin B6 on semen quality and testicular function

Wistar male rats injected high doses (≥ 125 mg kg-1 day-1) of pyridoxine hydrochloride for six weeks had lower weights of the epididymis, and lower weights of the testis, prostate gland, and seminal vesicle, and decreased mature spermatid counts at □ 500 mg kg-1 day-1[7]. In addition, at 1000 mg kg-1 day-1 dose, the activity of testicular enzymes such as LDH-X, a lactate dehydrogenase enzyme, activity was significantly decreased [8], whereas cytochrome P-450 and cytochrome b5 content, and beta-glucuronidase activity were significantly increased[9]. Histological investigations by the same group showed degeneration of elongated spermatids, delay in spermiation, Sertoli cell alterations, and germ cell degeneration at 500 mg kg-1 day-1 and 1000 mg kg-1 day-1[10].

In a different way, at 125 and 250 mg kg-1 day-1 (5 times per week for 6 weeks), sperm motility and count of Wistar rats were significantly decreased[9,11]. Moreover, at 250 and 500 mg kg-1 day-1 for 2 weeks' treatment, only very slight histopathological changes were observed[9]. While, at the same doses, but for 4- and 6-week treatments, decreased sperm motility, fertility index, epididymis weight, testicular proteins, and some histopathological alterations in the testes such as germ cells degeneration were observed[12].

Further, SD-Slc male rats at six-week of age treated intraperitoneally for four weeks with pyridoxine in saline at 500 mg kg-1 day-1 had sperm morphological and physiological changes (i.e., sperm motility)[13]. Sperm motility and morphology markedly decreased in male rats treated with pyridoxine after 4-9-week treatment [14]. In addition, after 4 weeks, histological change in the testes confirmed by a reduction in sperm count was observed leading to a marked testicular atrophy at 8-9 weeks[14].

In humans, pyridoxine was found to be present in seminal plasma, and that it is inversely associated with the ejaculate volume[15]. In addition, pyridoxal-5' phosphate was found to activate the monoamine oxidase (MAO), an enzyme that catalyzes the oxidation of monoamines (deamination), in human semen[16]. It is important to mention that the activity of monoamine oxidase was found to be higher in infertile men compared to fertile [16].

DISCUSSION

Effect of Vitamin B6 on seminal homocysteine

Vitamin B6 acts as a coenzyme for cystathionine-□-synthase enabling the transsulphuration of homocysteine into cystathionine and cysteine[17,18]. A deficiency in vitamin B6 causes accumulation of homocysteine or hyperhomocysteinemia[19,20]. It was reported that B vitamin deficiencies, including vitamin B6, are linked with hyperhomocysteinemia and gonadal abnormalities in males, such as altered spermatogenesis[19,21]. Therefore, normal levels of vitamin B6 in men seems important to protect the integrity of semen quality and maintain normal sperm parameters. Though, this suggestion requires more investigation, mainly by clinical studies.

Vitamin B6 and gonadal function

In 1984, Symes and co-workers have shown that vitamin B6 has a function in the action of steroid hormones, mainly testosterone, and vitamin B6 deficient male rats have a reduced synthesis of testosterone[22].

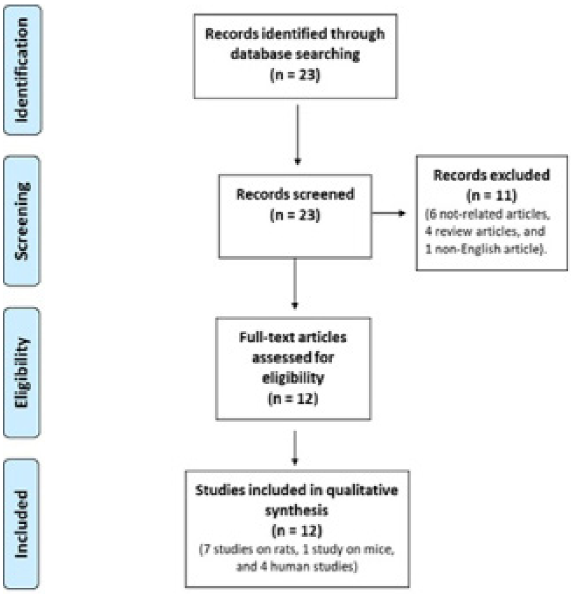

Figure 1. Literature search and selection diagram.

The mechanism by which this occurs is may be by recycling the testosterone receptors from the nucleus into the cytosol after primary translocation[22]. Later study has confirmed these results and found that vitamin B6 deficiency may alter in gonadal function since it is involved in synthesis of testosterone, follicle-stimulating hormone, and luteinizing hormone[23]. Another in vivo system study, in male rats, showed that the depression of gonadal development kept in constant darkness was improved by receiving normal amounts of vitamin B6 and vitamin B1, and a high amount of pantothenic acid [24]. Therefore, this evidence may indicate a valuable role of vitamin B6 in maintaining normal gonadal function, and hence normal semen quality.

Vitamin B6 in oxidative stress conditions

Vitamin B6 has been found to have potent antioxidant activity[25-27]. Compared to vitamins C, pyridoxine appears to quench singlet oxygen radical[25]. Mechanistically, it has been shown that the chromophoric moiety (3-hydroxypyridine) of vitamin B6 establishes an exceptional model that mimics the dynamic behavior of this vitamin as an antioxidant against riboflavin-generated reactive oxygen species[28]. For instance, the protein lysozyme was photo-protected by vitamin B6 from riboflavin-sensitized photo-degradation[28].

Further, independently of the homocysteine-lowering effect, it has been reported that patients with acute ischemic stroke supplemented B-vitamins, including vitamin B6, had lower oxidative stress, an imbalance between pro-oxidants and antioxidants to the favor of the former[29], indicating the immediate antioxidant activity of these vitamins[30]. Therefore, given that higher levels of free radicals, particularly reactive oxygen species, in semen lead to oxidative stress, and thus to sperm injury [31-33], then vitamin B6, once normally present in semen, may enhance the molecular defense mechanism against oxidative damage to sperm, thereby protects the normal sperm physiology, particularly sperm motility. Though, further research studies in this context seem important to endorse this suggestion.

Moreover, Glutathione system, including glutathione, glutathione reductase, and glutathione peroxidase, was found to be present in mammalian and human semen [34,35]. The function of this system appears to neutralize free radicals and protect the sperm against oxidative injury[34,35]. It is well known that vitamin B6 deficiency affects glutathione level and reduces the glutathione/oxidized glutathione ratio in the blood[36-38]. It has been recognized that the intracellular sperm glutathione system is altered in infertile men compared to fertile[39]. Based on this evidence, vitamin B6 deficiency may alter glutathione system, thereby affecting the antioxidant defense mechanism against oxidative damage to sperm, which may ultimately alter sperm parameters.

Seminal monoamine oxidase

It has been shown that adding monoamine oxidase to human semen in vitro induced seminal plasma cytotoxicity, which may affect negatively semen quality[40]. Given that pyridoxal-5' phosphate activates the monoamine oxidase enzyme[16], then adding pyridoxal-5' phosphate to human semen is suggested to trigger semen toxicity, which may lead to sperm injury.

CONCLUSIONS

Only from rodent studies (8 studies), it is obvious that high doses of vitamin B6 impair semen quality, mainly sperm count and motility, and cause significant histopathological changes such as germ cells degeneration. In humans, vitamin B6 has been approved to be present in normal semen, even though the available studies failed to show its direct relationship with normal sperm parameters. While, indirectly, it is suggested that a deficiency in vitamin B6 may lead to hyperhomocysteinemia, which may alter sperm parameters. In addition, it can be suggested that vitamin B6 may enforce the seminal antioxidant reservoir, which could be favorable to sperm function. Still, in vitro and clinical studies that investigate the direct effect of vitamin B6 on semen quality appear significant, and may contribute to the etiology of male subfertility.

DECLARATION OF INTEREST

The author declares no conflict of interest. The corresponding author alone is responsible for the content and writing of this work.

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