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Effects of Excess Vitamin B_6 Intake on Serum Lipid Profile and Cerebral Cortex in Rats

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Aim: The present study was undertaken to investigate the effects of dietary excess of vitamin B_6 on certain blood parameters [serum total cholesterol, high density lipoprotein (HDL) cholesterol and total lipid] and the cerebral cortex.

Materials and Methods: A total of 36 albino rats were included in the study. Saline solution was administered to control groups (CG-10, n = 6 for 10 days; CG-15, n = 6 for 15 days; CG-20, n = 6 for 20 days). The experimental groups (EG-10, n = 6; EG-15, n = 6; EG-20, n = 6) received 5 mg/kg vitamin B_6 daily for 10 days, 15 days and 20 days, respectively. Serum total cholesterol, HDL cholesterol and total lipid levels were measured and compared in CGs and EGs. The cerebral cortex tissue samples were examined by electron microscopy.

Results: The total serum cholesterol levels were significantly lower ($P < 0.05$) although serum HDL levels were significantly higher ($P < 0.01$) in all EGs. Total serum lipid levels were higher in EG-15 and EG-20 groups than in CGs. The structural degenerations in the perikaryon and neuropil were found prominent in EG-15 and EG-20 groups but not in EG-10. Marked damage in the neuronal and neuropilic structure was observed in rats who received long–term high doses of vitamin B_6. Based on these results, a relationship between cerebral cortex damage and serum total lipid and HDL levels in the EG-15 and EG-20 groups is suggested.

Conclusions: Dietary excess of vitamin B_6 intake reduces serum total cholesterol levels, but not serum HDL and total lipid levels, and also causes cerebral cortex damage in long-term treatment. Thus, a careful diet plan and monitoring of vitamin B_6 dose are recommended in patients who are supplemented with this vitamin.

Key Words: Vitamin B_6, blood, cholesterol, rat, cerebral cortex

Sıçanlarda Yüksek Doz Vitamin B_6'nın Serum Lipid Profili ve Serebral Korteks Üzerine Etkileri

Amaç: Bu araştırma, yüksek dozda alınan vitamin B_6'nın bazı kan parametreleri (serum total kolesterol, HDL kolesterol ve total lipid) ve serebral korteks üzerine etkilerini araştırmak için yapıldı.

Yöntem ve Gereç: Çalışmada total olarak 36 albino sıçan kullanıldı. Kontrol gruplarına (KG-10, n = 6; KG-15, n = 6; KG-20, n = 6) sırasıyla 10, 15, 20 gün sürelerle srum fizyolojik uygulandı. Deney gruplarına (DG-10, n = 6; DG-15, n = 6; DG-20, n = 6) sırasıyla 10, 15 ve 20 gün süreyle her gün 5mg/kg vitamin B_6 verildi. Serum total kolesterol, HDL kolesterol ve total lipid düzeyleri ölçüldü kontrol grupları ile deney grupları kıyaslandı. Tüm grupların serebral korteks dokuları elektron mikroskopla incelendi.

Bulgular: Bütün deney gruplarında total serum kolesterol düzeyleri anlamlı olarak düşük ($P < 0.05$) olmasına karşın, serum HDL düzeyleri anlamlı olarak yüksekti ($P < 0.01$). Bazı deney gruplarında (DG-15 ve DG-20) total serum lipid düzeyleri kontrol (KG) gruplarından daha yüksekti. Nöropil ve perikaryonda yapısal dejenerasyon belirgin olarak DG-15 ve DG-20 gruplarında bulunmasına karşın DG-10 grupta gözlenmedi. Uzun süre vitamin B_6 uygulanan deneklerde nöronal ve nöropilik harabiyet belirgindi. Böylece, DG-15 ve DG-20 gruplarında, serebral korteks harabiyeti ile serum total lipid ve HDL düzeyleri arasında bir ilişki olduğu ileri sürülebilir.

Sonuç: Yüksek dozda vitamin B_6 diyeti alındığında, serum total kolesterol düzeyleri düşer, fakat serum HDL ve total lipid düzeyleri düşmez. Uzun süre vitamin B_6 uygulamaları serebral kortekste harabiyete sebeb olur. Böylece, hastalara tavsiye edilen vitamin B_6 diyeti ve dozu planlanırken çok dikkatlı olunmalıdır.

Anahtar Sözcükler: Vitamin B_6, kan, kolesterol, sıçan, beyin/serebral korteks

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Introduction

Nutritional deficiencies have been documented to affect cellular differentiation during development. Several cognitive dysfunctions have been reported in subjects with nutritional deficiencies in basic elements, including pellagra syndrome, depression, irritability, confusion and disorientation resulting from niacin deficiency, and Wernicke-Korsakoff syndrome resulting from thiamine deficiency. Vitamin B_6 has been shown to be important for normal cognitive function and in lowering the incidence of coronary heart disease among the elderly (1,2,3).

The effects of malnutrition on organogenesis are well documented (4,5), even though discussion on the basic mechanisms still continues (6-10). The morphological changes observed in developing brain regions associated with maternal vitamin B_6 deficits were reported in rodents (4,11). Gutierrez-Reyes et al. (12) have indicated that malnutrition of vitamin B_6 also causes changes in memory efficiency in rats.

Dysfunctions in the immune system are related to malnutrition status (13). Structural cell changes in different organs associated with maternal vitamin B_6 deficiency have been reported during development. It has been suggested that vitamin B_6 restriction during gestation periods was a potential risk factor for a defect in synaptogenesis and neural differentiation (14,15). During pregnancy and lactation, this deficiency altered the function of N-methyl-D-aspartate receptors, important glutamatergic compounds involved in learning and memory (16).

Vitamin B_6 is also very important for the normal function of multiple organ systems. Previous studies have reported that high dietary intake of vitamin B_6 has some metabolic effects. The physiologically active forms of vitamin B_6 are enzymatic cofactors in many reactions of mammalian metabolism, including the metabolism of most amino acids and neurotransmitters (17). Indeed, it has been shown that there was a substrate-cofactor interaction between dietary histidine or tryptophan and vitamin B_6. Therefore, pyridoxine causes a clear interaction between substrate and coenzyme. The precursors influence the metabolism of histamine and serotonin (18). There are also some strong data supporting the idea that putative monoamine neurotransmitters, such as dopamine (DA), norepinephrine (NE), serotonin (SHT) and gamma amino butyric acid (GABA), are formed through decarboxylation of precursor amino-acid derivatives. It has also been known that pyridoxine has an important role as a crucial enzymatic cofactor in many reactions in the metabolism of neurotransmitters in the nervous system (9).

Vitamin B_6 is involved not only in the metabolism of amino acids and neurotransmitters but also lipids. It seems to be involved in some defense mechanisms against lipid peroxidation in tissues. Among factors which prevent lipid peroxidation, vitamin B_6 deficiency increased this process (19,20) when animals were fed hyperlipidic and totally vitamin B_6–deficient diets (21). Jain et al. (22) have suggested that vitamin B_6 is currently associated with an inhibitory effect on lipid peroxidation caused by free radicals derived principally from oxygen. When these radicals reacted with biological molecules, they caused biochemical damage at cellular level (23).

Some recently published works also showed the antioxidant potential of vitamin B_6 in the liver (24,25,26). It has been previously demonstrated that vitamin B_6 deficiency causes an increase in the peroxidizability level in some tissues (24). Maranesi et al. (27) showed that vitamin B_6 deficiency caused hypertrophic swelling of the kidney; lipid contents decreased in kidneys of rats fed vitamin B_6- deficient diets in comparison with those fed normal vitamin diets. It also caused a decrease in plasma proteolipid protein peptide (PLP) contents in comparison with normal vitamin conditions.

Thus far, experiments on dietary excess of vitamin B_6 have been inadequate. Dietary administrations of excess vitamin B_6 related to different aims under different daily doses have suggested that excess of vitamin B_6 affects the brain and serum concentrations of some amino acids and serotonin receptors (9,28,29,30,31,32).

Sermet et al. (33) have reported plasma lipoprotein levels and their relationship to atherogenic risk, and studied the feasibility of therapeutic doses of vitamin B_6 in rats with hypertension. Dietary vitamin B_6 supplementation attenuated increases in systolic blood pressure and tissue aldehyde conjugates (34). On the other hand, Aybak et al. (35) suggested that there was a relationship between pyridoxine status and arterial blood

pressure in essential hypertensive patients. Most published works on vitamin B_6 are limited to general clinical observations and case studies. Some of the studies (9,28,29,30) directed at the effects of high-dose vitamin B_6 administration have been discussed, but the limited number of the studies on the subject led us to investigate the effects of excess vitamin B_6 on serum lipid profile and the cerebral cortex.

The purpose of this study was to investigate whether high doses of vitamin B_6 affect the levels of serum total cholesterol, high density lipoprotein (HDL) cholesterol and total lipid level, and especially to compare the cholesterol levels of control and experimental groups in a time-dependent manner. Additionally, we studied the alterations in the fine structure of the cerebral cortex by electron microscopy.

Materials and Methods

Experiments

The study protocol was approved by the Akdeniz University Animal Care Center. Since there is a difference in nerve conduction velocity between males and females (36), we used only healthy male albino rats obtained from the animal care center of the Medical Faculty of Akdeniz University. Animals were housed in groups of four rats in stainless steel cages under standard conditions (24 ± 2°C and 50 ± 5% humidity) with a 12 h light-dark cycle (37). Six rats were used for each of three control groups (CG-10, CG-15, CG-20; total = 18) and three experimental groups (EG-10, EG-15, EG-20; total = 18). Thus, totally 36 Swiss Albino rats weighing 200-250 g were used for the study. The National Research Council (NRC) recommends a 7 mg/kg dose for vitamin B_6, dissolved in physiologic saline solution (0.9% NaCl), but previous studies administered higher than the recommended doses (30,31). The dose chosen in this study (5 mg/kg) is similar to that applied in previous studies (33,35). Vitamin B_6 (5 mg/kg/day) was injected intraperitoneally (IP) to the experimental groups EG-10, EG-15 and EG-20 for 10, 15 and 20 days, respectively. Physiologic saline solution was injected for 10, 15 and 20 days to the control groups, CG-10, CG-15, CG-20, respectively. Treatments for all groups, including daily doses and time periods, are summarized in Table 1.

Table 1. Doses of daily administered vitamin B_6 and saline according to experimental groups (EGs) and control groups (CGs).

Groups	Experiment period (days)	Daily dose
EG-10 (n = 6)	10	5 mg/kg vitamin B-6
CG-10 (n = 6)	10	5 mg/kg 0.9% NaCl
EG-15 (n = 6)	15	5 mg/kg vitamin B-6
CG-15 (n = 6)	15	5 mg/kg 0.9% NaCl
EG-20 (n = 6)	20	5 mg/kg vitamin B-6
CG-20 (n = 6)	20	5 mg/kg 0.9% NaCl

Ultrastructural analysis

Samples of brain tissues were fixed by immersion in 2.5% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4) at room temperature for 4 h and post-fixed in 1% phosphate-buffered osmium tetroxide for 2 h. The specimens were dehydrated in increasing concentrations of ethanol and embedded in araldite-epoxy resin. Semi-thin sections were stained with toluidine blue. Ultra-thin sections were double-stained with uranyl acetate and lead citrate (38,39).

Blood sample analysis

The blood samples were collected from each group via cardiac puncture. The levels of total cholesterol, HDL cholesterol and total lipid index in serum were determined in a Dacos Autoanalyzer using enzymatic Dort reagents (Counter Inc Hielab, Miami, USA). Total cholesterol, HDL cholesterol and total lipid level in different EGs were compared with each other and CGs.

Statistical analysis

The statistical evaluation for blood parameters was done by Student's t-test, comparing each group with its control group. The results of blood parameters were normally distributed (as tested by Kolmogorov-Smirnov test) throughout the experiment days. Analysis of variance (ANOVA) and the Tukey test were carried out for statistical analysis and pair wise multiple comparisons. Statistical calculations were performed using Sigmastat for Windows, version 2.0 (Jandel Scientific Corporation, San Rafael, CA, USA).

Results

There was no significant difference between the mean of body weights of standard fed rats, which were weighed at the end of the experimental periods (CGs: 220 ± 15; EG-10: 230 ± 25; EG-15: 225 ± 30; EG-20 240 ± 20).

Blood parameters

HDL cholesterol, total cholesterol and total lipid levels were determined for all CGs. No significant differences were observed among the CGs for these values. Thus, the mean values for each parameter of the three control groups were accepted as the normal values and compared with the mean values of each parameter in EGs (Table 2).

The blood levels of total lipid, total cholesterol and HDL cholesterol according to EGs and CGs are presented comparatively in Table 2.

Serum HDL cholesterol was 34.2 ± 4.3 mg/dl in the CGs (the mean value of 3 CGs) and it was significantly higher in vitamin B_6 (5 mg/kg/day) administered rats (Table 2). HDL cholesterol levels were 40.98 ± 6.39 mg/dl in EG-10, 47.18 ± 4.04 mg/dl in EG-15 and 44.29 ± 5.37 mg/dl in EG-20. However, total cholesterol was 61.2 ± 12.4 mg/dl in CGs (the mean value of 3 CGs), and it decreased significantly to 52.15 ± 5.33 mg/dl in EG-10, 54.64 ± 5.86 mg/dl in EG-15 and 48.32 ± 6.95 mg/dl in EG-20.

Total lipid level was 160.8 ± 32.6 mg/dl in the CGs (the mean value of 3 CGs) versus 148.33 ± 34.69 mg/dl in EG-10, 181.95 ± 20.23 mg/dl in EG-15 and 182.09 ± 37.82 mg/dl in EG-20.

The comparisons of the blood parameters regarding each EG are presented in Table 2. According to the analysis, there were significant differences in serum total lipid levels between EG-10 and EG-15 and also between EG-10 and EG-20 ($P < 0.05$), but there was no significant difference between EG-15 and EG-20.

There was a significant difference between EG-15 and EG-20 with respect to serum total cholesterol levels. On the other hand, HDL cholesterol levels were also different in EG-10 and EG-15 ($P < 0.05$).

Ultrastructural observations

Control groups

Structural features of the cerebral cortex elements including neuropil, fibrillar architecture and neurons with myelinated or unmyelinated nerve processes were observed in normal condition (Figure 1).

Experimental groups

Increased cytoplasmic density and vacuolization, expansion of the Golgi complexes and the partial mitochondrial cristae loss in the perikaryon were observed depending on the duration of vitamin B_6 administration. When CGs were compared with EGs, cytoplasmic organelles and nucleus with prominent

Table 2. Blood parameters from experimental groups (EGs) treated with high- dose vitamin B_6. The effects of vitamin B_6 administration on serum cholesterol and lipid levels are comparable between EGs and control groups (CGs).

	HDL cholesterol (mg/dl)	Total cholesterol (mg/dl)	Total lipid (mg/dl)
CGs mean value	34.2 ± 4.3	61.2 ± 12.4	160.8 ± 32.6
CG-10 (n = 6)	32.8 ± 3.28	64.61 ± 13.9	158.56 ± 31.85
CG-15 (n = 6)	34.6 ± 4.39	61.67 ± 12.1	163.28 ± 33.71
CG-20 (n = 6)	35.3 ± 5.1	60.3 ± 11.2	160.41 ± 32.33
EG-10 (n = 6)	40.98 ± 6.39**	52.15 ± 5.33*	148.33 ± 34.69
EG-15 (n = 6)	47.18 ± 4.04***	54.64 ± 5.86*	181.95 ± 20.23***
EG-20 (n = 6)	44.29 ± 5.73**	48.32 ± 6.95**	182.09 ± 37.825***

EGs versus CGs *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$.

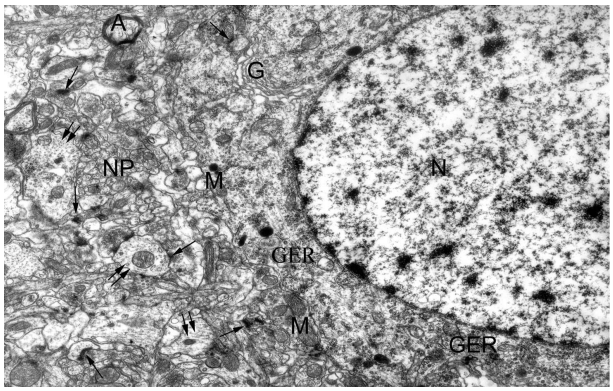

Figure 1. A pyramidal neuron with cytoplasmic organelles and euchromatic nucleus (N) and neuropil (NP) are seen in this figure from the control group. Subcellular components of perikaryon and NP with synaptic points (arrows) are clearly observed. Granular endoplasmic reticulum (GER), Golgi complex (G), mitochondria (M), lipofuscin granule (Lf), myelinated axon (A), and unmyelinated axon (with double arrows) are shown. CG; x 20,750.

nucleoli in the perikaryon were found in normal condition in EG-10. Myelinated nerve fibers in EG-10 were also normal but vesicles were formed in unmyelinated nerve fibers (Figure 2). In addition to these differences, interdigitated nucleus with heterochromatic substance, excessive cytoplasmic damage, organelle loss, neuropilic edema, vacuolization and nerve fiber demyelinization were observed in EG-15 and EG-20 groups. These structural degenerations in the perikaryon and neuropil

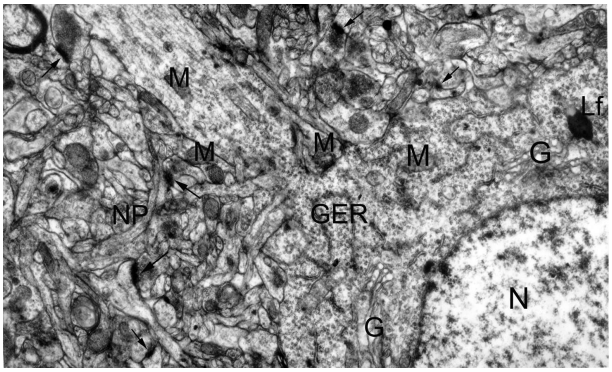

Figure 2. Perikaryon with slightly deformed shape of subcellular components with euchromatic nucleus (N) including fine chromatin is seen. Dilated Golgi complex (G), partially damaged mitochondria (M) with partial crystal resolution, electron dense lipofuscin pigment granules (Lf), and widespread Nissl bodies are observed. In neuropil, a compact-like architecture, rare synaptic points (arrows) and myelinated as well as unmyelinated axon and dendrite sections are seen. EG-10; x 25,000.

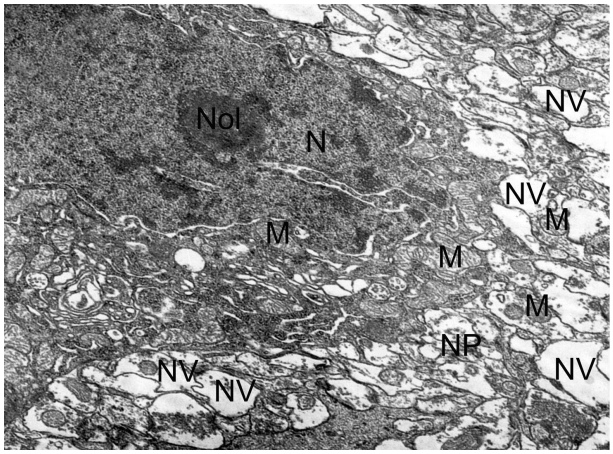

Figure 3. Due to the effect of high doses of vitamin B_6 treatment for 15 days, cellular and neuropil damage, heterochromatic nucleus (N) with nucleolus (Nol) and electron dense cytoplasm with vacuoles, canal-like cisternae (arrows) and many damaged cell organelles are seen. This electron micrograph shows typical neuronal and neuropil (NP) damage with long-term high doses of vitamin B_6 treatment. Many neuropil vacuoles (NV) and edema areas and very rare synaptic points (double arrows) are seen. EG-15; x12.500.

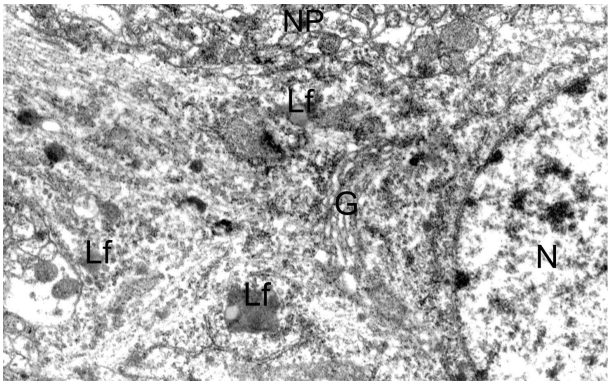

Figure 4. A typical damaged pyramidal neuron with irregular shape and deformed axonal hillock process are seen in cerebral cortex from EG-20. Excessive dilatation of the Golgi complexes (G) and excessively increased electron dense lipofuscin (Lf) pigment granules and multivesicular bodies are seen. Increased amount of damage in cell organelles is prominent finding. Heterochromatic nucleus (N); EG-20; x 25,000.

were the most prominent features of the EG-15 and EG-20 (Figures 3 and 4) groups, but not of EG-10. The rats which were treated with long–term high doses of vitamin B_6 showed prominent damage in the neuronal structure and neuropilic architecture. In the axonal structure, typical demyelinization and neurofilament network were observed (Figure 5).

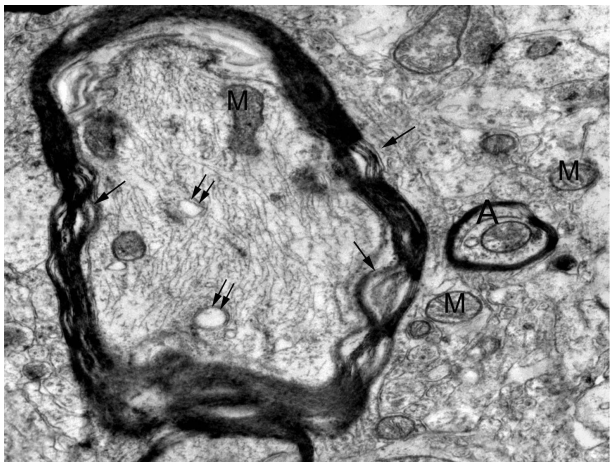

Figure 5. High magnifications of an axon showing prominent demyelinization; some vesicular bodies in axoplasm with neurofilament network are seen in EG-20, x 48,000.

Discussion

For the past two decades, there have been suggestions that abnormalities in cellular function might be related to vitamin B_6 deficiency. Vitamin B_6 is closely related with the permeability of the cellular membranes and a secondary interaction takes place between the intracellular Krebs cycle and cholesterol levels. For instance, in vitamin B_6 deficiency, labeled acetate influxes are 10- fold higher into the cholesterol in the liver. It has been reported that hepatic cholesterol synthesis is stimulated and the activity of the Krebs cycle is decreased in vitamin B_6 deficiency (40,41). Major and Goyer (42) have reported decreased cholesterol levels with additional vitamin B_6 therapy in patients with alcoholism who were previously treated with disulfiram and who had high cholesterol levels. Recently, it has been suggested that vitamin B_6 could attenuate domoic acid that induced glutamate increase and extracellular calcium influx. It is also reported that domoic acid enhanced induction of some oncoproteins and could regulate neuroprotective actions mediated through current therapeutic strategies (6). The administration of high doses of vitamin B_6 is effective in the suppression of hepatic cathepsin B activity (43). In a study with dialysis patients who were supplemented with vitamin B_6, a reduction in homocysteine levels and improvement in the lipidemic profile of the patients were reported (44).

Dietary excess of vitamin B_6 supplementation supports the hypothesis that aldehydes are involved in increased systolic blood pressure, thus vitamin B_6 may be an effective antihypertensive molecule (34). Since pyridoxal phosphate is a physiological antagonist of glucocorticoid activity, the prenatal administration of excessive vitamin B_6 suggests that this vitamin may counteract glucocorticoids with respect to fetal growth risk. It has been also suggested that vitamin B_6 deficiency causes changes in glucose metabolism and skin collagen neogenesis (45). A deficiency of vitamin B_6 caused a decrease in the levels of vitamin B_6-dependent enzymes, such as ornithine aminotransferase, alanine aminotransferase, and aspartate aminotransferase, which also contribute to gluconeogenesis (45).

On the other hand, it was reported that there was no association between serum lipids and vitamin B_6 in healthy persons, in patients who are hospitalized for cardiac surgery and in patients without clinical evidence of atherosclerosis (46). Another study revealed that the increase in blood cholesterol determines the membrane cholesterol, which in turn influences the permeability of neuron membrane, thus altering several functions including transport processes (47, 48). In light of these recent studies, we may speculate that if the Krebs cycle is inhibited and cholesterol synthesis is increased in case of vitamin B_6 deficiency, then the contrary should also be true. In other words, excessive vitamin B_6 may lead to increased Krebs cycle activity by inhibiting cholesterol synthesis (49).

The results of our recent study (39) showed that long-term administration of high doses of vitamin B_6 caused cellular and neuropilar damage and loss of some cellular organelles in the cerebral cortex. In addition, the pyramidal neurons suffered proportional atrophy of cellular processes and components. The granular endoplasmic reticulum (GER) showed regional hyperplasia relative to the control groups, but fine structural analysis did not indicate which metabolic steps were affected. As with the GER, the mitochondria also showed hyperplasia, and there were increased lipofuscin granules in the perikaryon as well as in the neuropil. In addition, vacuolation and edema were observed due to the loss of cellular processes and damaged neuropilar architecture. The hyperactivity of the nuclei and nucleoli also indicated that there was an induction of protein synthesis.

Previously, Schaeffer et al. (9, 31) reported no neurotoxicity depending on behavior action, but effects

on amino-acid concentration and binding properties of cortical serotonin receptor in brain tissue with high daily doses of vitamin B_6 intake.

The findings of the present study suggest that long-term administration of high doses of vitamin B_6 is likely to result in intracellular biochemical imbalance and decrease in serum cholesterol levels. Kannan et al. (49) demonstrated that vitamin B_6 compounds can prevent the oxygen radical generation and lipid peroxidation caused by hydrogen peroxide in U937 monocytes, and that some of the protective effect of vitamin B_6 may occur via modification of mitochondrial function. Parallel to those findings, our objective results such as partial loosening of the mitochondria, vesicular vacuoles in the myelinated or unmyelinated axons, severe dilatation of Golgi complexes in the perikaryon, and formation of wider vacuoles in place of the damaged neuropil with local edema formation (39) have suggested the alterations in membrane permeability and imbalanced cell cytophysiology.

Harripersad and Burger (50) have showed that a subnormal intake of vitamin B_6 made no significant difference in the HDL levels, although it contributed to a significant increase in low density lipoprotein (LDL) and total cholesterol levels. According to the results of our study, the alteration in serum cholesterol levels, total lipid levels and HDL cholesterol levels, which were observed in the vitamin B_6 treated EGs, were disproportionally fewer than those observed in vitamin B_6 deficiency (15,51,52,53). However, serum cholesterol levels were decreased in the EGs receiving excessive vitamin B_6 for long periods.

It has been shown that vitamin B_6 deficiency caused decreases in lipid contents in kidneys of rats fed vitamin B_6-deficient diets in comparison with those fed normal vitamin diets (27,54). It also caused a decrease in plasma PLP contents in comparison with normal vitamin conditions. In agreement with those data, our results showed that lipid levels were increased significantly in EGs, as there were significant differences in serum total lipid levels between EG-10 and EG-15 and also between EG-10 and EG-20, but there was no significant difference between EG-15 and EG-20. Total serum cholesterol levels were significantly different between EG-15 and EG-20 and serum HDL cholesterol levels were also different in EG-10 and EG-15. In other words, serum total cholesterol and HDL cholesterol levels changed in a time-dependent manner.

In the CGs, the fine structure of the cortex neurons and fibrillary architecture of the neuropil showed great similarity with our recent study (39). Dendrite processes establish the synapses that are the contact points of the neurons. Thus, one can conclude that neural tissue with poor dendrite processes would suffer from malfunction and loss of interconnection. In our recent study, decreased synaptic points were observed in cerebral layers due to high doses of vitamin B_6 treatment for an extended period; this could result from disorientation between dendrite processes and may affect the functional condition of synaptic fields. The number of myelinated axons, as determined by electron microscopy, was decreased in the cerebral cortex and there was decreased specific activity of myelination of the total brain (39). Thus, the functional consequences of dietary excessive vitamin B_6 intake for a long period or even with recommended doses may be through reduced serum cholesterol levels and decreased total lipid in blood. Therefore, we may speculate that high doses of B_6 intake for a long time cause neurotoxicity. However, this idea is consistent with the hypothesis that high doses of vitamin B_6 administration should cause low serum cholesterol levels and so less damage in membrane permeability. These results demonstrated that long-term administration of high doses of vitamin B_6 caused marked structural damage and cellular intoxication in cerebral cortex neurons. The therapeutic approach of long–term high doses of vitamin B_6 administration decreased total serum cholesterol and increased HDL cholesterol, but it also caused neurotoxicity.

In conclusion, excessive vitamin B_6 administration with increasing treatment periods is likely to alter serum lipid levels. The comparative analyses of serum lipids have shown that while serum HDL cholesterol and total lipid levels increased significantly, total cholesterol levels decreased as the vitamin B_6 treatment period was extended. In addition, we observed prominent cerebral cortex degeneration in treatment extension. In routine clinical practice, vitamin B_6 is used in patients with peripheral neuropathy, including entrapment neuropathies, even without an evidence of deficiency. Most of the time patients continue to receive vitamin B_6 even for years. Thus, one should pay careful attention to the administration time and vitamin B_6 dosage

recommended for patients who are supplemented with this vitamin. Careful diet planning and supplementation and permanent monitoring of vitamin B_6 in the serum are very important in patients with elevated risk of different pathologies.

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