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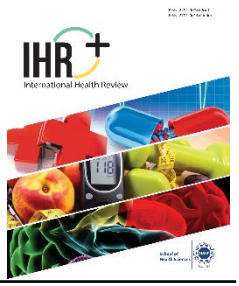

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Effect of Vitamin B12 Supplementation on the Diabetic Peripheral Neuropathy-A Narrative Review

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Abstract

The unpleasant sensation felt due to lesions of nerves is known as Neuropathic pain. It is found to be common in individual suffering from type I and II diabetes, as changes in blood glucose levels could affect the nervous system severely. Additionally, the large intake of metformin for a long period of time hinders the normal absorption and metabolism of vitamin B12 in the body which results in vitamin B12 deficiency. Vitamin B12 is responsible for the methylation process in body. Hence, it is essential for myelin sheath production and DNA synthesis. Vitamin B12 deficiency takes a toll on the nerves which may result in neuropathy. In this review, the up-to-date data has been summarized to appraise the effect of Vitamin B12 on nerve regeneration and whether its supplement could be used in order to improve the diabetes-induced peripheral neuropathy.

Keywords: blood glucose level, diabetes-induced peripheral neuropathy, neuropathic pain, neuropathy, vitamin B12

Introduction

Vitamin B-12

Vitamins play a vital role in human growth and development. One of the most complex vitamins found in the human body is vitamin B12, also known as cobalamin. It has a corrinring and its structure is found to be similar to hemoglobin and chlorophyll. Cobalt is used at the active site of vitamin B12 where it forms a bond with various groups, that is, cyano, methyl, 5'deoxyadenosyl, and hydroxyl. Methyl and 5'deoxyadenosyl groups have a role in the catabolism of enzymatic reactions [1].

A common source of vitamin B12 is diet. In food, it is in bound form with protein and needs stomach acid along with pepsin to be released. After

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getting free, it makes a bond with intrinsic factor which is secreted from the stomach. This complex travels down the small intestine and gets absorbed there. In human body, the main focus of vitamin B12 is to catalyze the isomerase and methyl transfer reactions. As adenosyl cobalamin, vitamin B12 plays a crucial part in the isomerase reactions that involve methylmalonyl CoA mutase. These play an essential role in the metabolism of cholesterol, valine, methionine, threonine, and isoleucine. Methylcobalamin is utilized by methionine synthase as a methyl source. The respective methyl group combines with the homocysteine for the synthesis of amino-acid methionine. The methionine is further transformed to S-adenosyl methionine that has the role of methyl donor in methylation reactions. These reactions occur in human body, that is, DNA methylation, methylation of myelin basic protein (used in myelin sheath synthesis around nerves, hence, the deficiency of vitamin B12 may lead to degeneration of myelin sheath and subsequently nerve damage). Vitamin B12 is again recycled to its active methylated form by methyl-tetrahydrofolate [2].

Role of Vitamin B12 in Nerve Regeneration

Various animal studies explored the effect of vitamin B12 on regeneration with regard to the nerves. In recent research, the effect of single and combined therapies of vitamin B12 and vitamin D was studied on nerve injury (sciatic)in female rats (n=8). Resultantly, vitamin B12 was found to improve the healing of peripheral nerves at a dose 1mg/kg/day intra-peritoneal when given for four weeks. There was a significant improvement in Sciatic function index (SCI) and Oedema- Inflammation as compared to the control group [3].

Assessment of Vitamin B12

No standard guidelines are present to assess vitamin B12 levels. However, on the basis of evidence derived from case control and cohort studies, for those patients taking metformin for a large span of time, periodic screening of vitamin B12 levels is recommended by the 2021 American Diabetes Association Standards of Medical Care in diabetes [4].

A systemic review, studying the deficit of vitamin B12 and its interrelation to free radical damage in the human body revealed vast evidences confirming the antioxidant potential of vitamin B12. Vitamin B12 is one of the key modulators of redox homeostasis. Hence, its deficiency produces oxidative stress that results in many complications. Many animal studies are

conducted in this regard, however, due to the regulation of vitamin B12 status in rodents associated with microbialB12 synthesis, these studies may not be generalized to humans as they rely on dietary consumption of vitamin B12 entirely. Serum vitamin B12 levels are utilized most commonly, however, recent studies suggest that Hcy, MMA, and Holo-TCare are better indicators than serum vitamin B12 levels. It is important to work in order to develop a gold standard assessment for B12 levels [5].

Diabetic Neuropathy Pathways

Diabetes Mellitus affects more than 460 million individuals globally [6]. Due to the high demand for glucose in neurons, they are much more sensitive to fluctuations of glucose in the body and under the influence of insulin. Moreover, the episodic uptake of glucose by neurons is affected too. ATP obtained by the metabolism of glucose is used by neurons for physiological functioning. Hence, the disrupted metabolism of glucose due to diabetic hyperglycemia causes the glucose levels to increase up to four times the normal. This constant supply of extra glucose to neurons may result in neurological damage which is known as glucose neurotoxicity.

This extra glucose in the cell is converted to sorbitol by means of polyol pathway. Increased levels of sorbitol have the following consequences:

1) Myoinositol, which is essential for normal neural functioning, is effluxed due to altered osmotic balance caused by excess levels of sorbitol.

2) Conversion of glucose into sorbitol causes an increase in oxidative stress which plays a role in causing peripheral neuropathies in patients with diabetes.

3) Sorbitol production results in the depletion of nicotinamide adenine dinucleotide phosphate (NADPH) stores which are used in super-antioxidant glutathione regeneration. It affects the natural defense mechanism present in the body that works against oxidative stress.

Hypoglycemia also results in enhanced assembly of pyruvate which increases the voltage gradient over the inner lining of mitochondria which, in consequence, causes an increase in super-oxides levels, oxidative stress, and mitochondrial damage. The cellular capacity of ATP generation is also affected which induces the cellular apoptosis and neuronal deterioration [7].

Diagnosis and Prevention of the Diabetic Neuropathy

When diabetic patients show the indications of peripheral neural dysfunction without any apparent reason, it is termed as eddiabetic peripheral neuropathy. Commonly, the certainty of diagnosis depends on the severity of signs and symptoms. The diagnosis relies only on history and examination in most cases and more objective tests are used only for research studies. Symptoms of diabetic peripheral neuropathy include numbness, pain, tingling, weakness, and unsteadiness in the peripheries. Toronto Clinical Neuropathy Score (TCSS) or Michigan Diabetic Neuropathy Score (MDNS)is used to assess the clinical signs and symptoms.

According to the Canadian and American Diabetes Association (ADA), the screening of individuals with diabetes mellitus type II for neuropathy has to be done at the time of diagnosis and annually after that. Other than the monofilament test or vibration test, simple questionnaires and clinical examinations may be conducted to find out the severity level of neuropathy.

A common factor between type I and II diabetes is hyperglycemia. Studies show that glycemic control may have a significant influence on the management of diabetic neuropathy in individuals, particularly with type I diabetes. Diabetic patients are recommended lifestyle modification and routine exercise, however, the effect of exercise on neuropathy is still under investigation [8].

Metformin and Diabetic Neuropathy

The first-line treatment recommended for diabetes mellitus is metformin due to various reasons. Some of them have limited side effects, low cost, low rate of interaction with other drugs, lower hypoglycemia risk, and improvement of cardiovascular morbidity. Metformin acts as an insulin sensitizer by inhibiting the hepatic glucose synthesis, lowering glucose absorption in the intestine, and increasing fat sensitivity. However, long-term use of metformin may disrupt vitamin B12 absorption, causing its deficiency.

The functions of vitamin B12 in human body are not just vascular, hemopoietin, and neurocognitive, however, it also plays an essential role in energy production, metabolism of fat, and DNA synthesis. Metformin causes vitamin B12 malabsorption by disrupting the calcium-dependent membrane action of ileal cell membrane receptors which are responsible for

the uptake of intrinsic factor and vitamin B12 complex in the human small intestine. This causes vitamin B12 deficiency which further increases the homocysteine levels, leading to an increased probability of cardiovascular diseases [9].

The research conducted in Pakistan showed that vitamin B12 in-sufficiency prevalence may further extend to deficiency and the use of metformin in diabetic individuals for longer periods of time increases the risk of neuropathy [10].

The relationship between use of metformin and vitamin B12 levels was studied at the Central Military Hospital in Colombia and the effect of reduced B12 levels on neuropathy was also considered. Vitamin B12 and neuropathy levels were evaluated by using a chemiluminescence immunoassay and Michigan neuropathy screening instrument (MNSI), respectively. This study showed a significant relation between diabetes-induced neuropathy and low vitamin B12 levels. Moreover, it was determined that metformin intake at high dose affect the level of vitamin B12 in the body, especially in male patients and those suffering from diabetes. The only limitation was that this study did not consider if patients suffered from neuropathy before the use of metformin [11].

The association between vitamin B12 deficiency in humans and the use of metformin was further confirmed through an observational retrospective study conducted in Saudi Arabia on 412 subjects. In the current research, patients suffering from type II diabetes were treated with metformin and without it, and then these were assessed for neuropathy and vitamin B12 levels. It was established that 2000mg/day or more than 4 years of metformin use are linked with low serum vitamin B12. It was also observed that high dietary use of vitamin B12 had no protective effect on vitamin B12 deficiency in individuals taking metformin and subjects with low vitamin B12 levels also showed high levels of serum homocysteine [12].

In diabetic individuals presented with neuropathy, the use of metformin may worsen the situation. An observational case-control research study noted the influence of metformin on diabetic neuropathy among 120 individuals having both type II diabetes and diabetic peripheral neuropathy. Half of them were given metformin for 6 months, while the remaining half were given other anti-hyperglycemic drugs. It was observed that patients taking drug showed high homocysteine and low plasma cobalamin. They

also showed a high frequency of neuropathy. The severity of peripheral neuropathy was determined to be positively correlated with homocysteine levels. Higher doses and duration of metformin use along with the longer duration of diabetes were linked with a high occurrence of diabetic peripheral neuropathy [13].

Another randomized-controlled trial of diabetic patients, using insulin not only showed the association of metformin with low serum vitamin B12 levels, however, it also enhanced the methyl malonic acid (MMA) levels. Increases in MMA levels result in increased severity of neuropathy and worsen the symptoms [14].

Diabetic Peripheral Neuropathy and Vitamin B12

Can vitamin B12 supplementation really improve diabetic peripheral neuropathy or not, has been the topic of interest for researchers for a while. A recent double-blinded randomized trial in Greece studied subjects (n=90) suffering from type II diabetes mellitus and having metformin for a minimum of 4 years. Subjects suffering from the autonomic and peripheral neuropathy were randomly divided into two groups. One group of 44 subjects received the intervention of 1000mg/day of oral methylcobalamin for the period of one year and another group (n=46) received the placebo. The quality of life and the level of pain were assessed using the michigan neuropathy screening instrument examination (MNSIE) and the questionnaire (MNSIQ). They were also evaluated for sural nerve conduction velocity (SNCV), sural nerve action potential (SNAP), and vibration perception threshold (VPT). The raise in vitamin B12 levels in the plasma of subjects in the group, receiving intervention was observed in contrast with the control group. A positive effect was seen on SNAP, MNSIE, VPT, SNCV, quality of life, pain score, and sudomotor functions in patients treated with vitamin B12 [15].

The research studying the effect of methylcobalamin therapy was conducted on subjects (n=200) suffering from type II diabetes showing the symptoms of neuropathy and taking metformin for at least 6 months in Pune, India. The subjects were classified into three groups depending on their vitamin B12 levels considering normal vitamin B12 levels as >400 pg/ml, insufficient vitamin B12 levels as 250-100 pg/ml, and deficient vitamin B12 levels as less than 250 pg/ml. Furthermore, vitamin B12 deficient patients were assigned/classified into two intervention groups, that is, one of them

was treated with oral methylcobalamin tablet of 1500 mg/day for total of 180 days, while the other group was given methylcobalamin injection parentally 1000mcg/week for a period of 6 months intramuscularly. This study determined that both interventions lowered the severity of diabetic peripheral neuropathy effectively and no difference was observed between NTSS-6-scores of injections and oral supplements. Additionally, no correlation between duration of diabetes and vitamin B12 deficiency was found, however, there was a significant correlation between vitamin B12 deficiency and the dosage of metformin. Vitamin B12 was found to lower the severity of diabetic peripheral neuropathy significantly [9].

1.5mg methylcobalamin per day for 3 months in patients with diabetic neuropathy also showed a positive effect on neuropathy examination scores [16]. It is important to dig deep in order to study the synergic potential of vitamin B12 with other compounds and its effect on diabetic peripheral neuropathy. The combination of methylcobalamin with prostaglandin E1 carries a positive effect on nerve conduction velocity and it improves the clinically presented symptoms of diabetic peripheral neuropathy [17]. Similarly, the combined therapy of vitamin B12 with alpha lipolic acid have been found to improve the vibratory threshold, numbness, and prickling [18].

The effect of combination therapy of vitamin B12 along with superoxide dismutase lipolic acid and acetyl-N-Carnitine was studied in a double blind placebo-controlled study in Greece. The subjects (n=85) were diabetic and were treated with metformin dose >1500mg/day for a minimum period of four years and showed diabetic peripheral neuropathy. They were intervened with combination therapy (n=43) and placebo (n=42) for a period of 12 months. The results showed a significant improvement in vitamin B12 levels, pain, quality of life, sural nerve conduction velocity, and vibration perception threshold in the group receiving the combination therapy. While the parasympathetic nervous functioning further deteriorated in the placebo group which confirmed the synergistic effect of vitamin B12 with other compounds [19].

Route of the Administration

Oral and intra-muscular routes of administration are the most common for the cure of vitamin B12 deficiency, however, other routes of administration were also found effective [20].

A recent 12-week long randomized trial in Italy, studied the effect of 50 mg/day cyanocobalamin sublingually. It was determined to restore the concentration of vitamin B12 in serumamong vegetarians having a deficiency of vitamin B12 at borderline [21].

In another randomized-controlled trial held in China, corneal-confocal microscopy was used to compare the effect of mecobalamin oral tablets (n = 17) co-related to intramuscular injections (n = 15) in patients with diabetic peripheral neuropathy. Samples were equally divided into two groups randomly with one group receiving mecobalamin intramuscular injection (0.5 mg/day and 3 times/ week), while the other was treated with mecobalamin oral tablets (1.5 mg/day) for 8 weeks each. Injection treatment was found to improve the corneal nerve branch density, inferior whorl length, and corneal nerve fiber length (CNFL) significantly, while the oral tablets showed a positive effect on TCSS. Both treatments did not show any adverse effects. The small sample size and duration were the only limiting factors of this study [22].

Conclusion

The studies confirming the effect of vitamin B12 monotherapy on diabetic peripheral neuropathy are limited and carry many limitations, that is, small sample size, improvement of glycemic control during study, short follow-up period or neglecting the serum B12 measurements during the trial. Many of them have quite a short time period, hence, they do not consider the influence of B12 therapy on the human body in long run.

Metformin which is responsible for the deficiency of vitamin B12 is strongly evident by the vast body of literature which consequently leads to much neurological pathology. The patients, suffering from diabetes mellitus and taking metformin, periodic screening of Vitamin B12 levels is necessary and the development of a gold-standard diagnostic test is highly recommended. The current data suggests the modest effect of vitamin B12 to improve the signs and symptoms of diabetic peripheral neuropathy, however, further research with improved protocols is needed. Many studies showed the enhanced effect of vitamin B12 when used in combination with various other vitamins or compounds.

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