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A SYSTEMIC REVIEW ON THE IMPACT OF VITAMIN B6 DEFICIENCY ON THE SEVERITY OF DIABETIC PERIPHERAL NEUROPATHY

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ABSTRACT

Diabetic peripheral neuropathy is the commonest cause of neuropathy worldwide and the severity of neuropathic pain increases with increase in the duration of diabetes. Vitamin B6 is a water-soluble vitamin that is present in foods such as pork, poultry, oats, bananas, dark leafy green vegetables and is accessible in many dietary supplements. The deficiency of Vitamin B6 is considered as a risk factor for developing peripheral neuropathy. Pyridoxine strongly contributes to the proper functioning of the nervous system by facilitating neurotransmitters and myelin synthesis. Studies show that there is a decrease in serum Pyridoxal 5'Phosphate levels in diabetic patients when compared with healthy population which may contribute to glucose intolerance. Vitamin B6 supplements are used in management of diabetic neuropathy for its anti-oxidant property and which had indeed helped in reduction of painful symptoms of neuropathy. Vitamin B6 when taken in higher doses greater than daily requirement will causes neuronal damage as well.

KEYWORDS: Diabetes, VitaminB6, Neuropathy, Pyridoxine.

INTRODUCTION

Diabetes is one of the leading metabolic disorders of hyperglycemia which can be due to decreased insulin secretion, increased glucose production or decreased glucose utilization. One of the severe complications of diabetes is Neuropathy which is considered to be related to duration and severity of hyperglycemia[1]. More than 60% of patients with a history of diabetes greater than 15 years are at risk of developing neuropathic pain. Diabetic neuropathy can be defined as the presence of symptoms or signs of peripheral nerve dysfunction resulting in severe pain in lower and upper limbs[2]. Neuropathic pain generally begins in the toes bilaterally and then proceeds to feet and legs. After establishing in the lower limb completely the upper limbs are affected. Currently the treatment for painful neuropathy is for symptomatic relief which may not alter the disease process. The most commonly prescribed drug for neuropathic pain includes gabapentin, pregabalin and tricyclic antidepressants[3].

PATHOGENESIS OF DIABETIC NEUROPATHY

The pathogenesis of diabetic neuropathy is multifactorial and it differs between T1DM and T2DM. Increased glucose position in the blood for longer duration can affect the nerves in several ways.

Studies shows that there are four applicable mechanisms that show how hyperglycemia causes DPN in cases[4,5,6].

Increased Polyol Pathway Flux;

The polyol pathway thesis states the fact that hyperglycemia convinced increased flux through polyol pathway via enzyme aldose reductase performing in accumulation of sorbitol in nerves and therefore reducing the nerve conduction velocity[7].

Activation of Protein Kinase- C(PKC) Pathway

The functions of other proteins are controlled by the co enzyme protein kinase. Neuronal death occurs after transubstantiating growth factor B leading to vascular occlusion is a common medium for neuropathy and vascular disease[8].

Increased Advanced Glycated End- products conformation

Advanced Glycated End- products are formed as a result of hyperglycemia through non-enzymatic glycation of proteins therefore leading to the conformation of covalent bonds between proteins or lipids leading to intra and extracellular crosslinking and aggregation leading to injurious effect on nerves[9].

Increased Hexosamine Pathway Flux

In this pathway neuroinflammation associated with DPN occurs which is due to accumulation of extracellular matrix with hyperglycemia[10].

RISK FACTORS

The major threat factors for DPN include hyperglycemia, diabetes duration and insulin resistance followed by dyslipidemia and hypertension. Other threat factors include obesity, smoking and exposure to AGEs through food intake[11].

DIAGNOSIS

The differential diagnosis of neuropathy is a very crucial step. According to severity defined grades of DPN were defined by Toranto Diabetic Neuropathy Expert Group as[12,13].

• Grade 0: no abnormality of nerve conduction

• Grade 1a: abnormality of nerve conduction without symptoms or signs

• Grade 1b: nerve conduction abnormality of stage 1a plus neurologic signs typical of DSPN, but without neuropathy symptoms

• Grade 2a: nerve conduction abnormality of stage 1a with or without signs (but if present, <2b) and with typical neuropathic symptoms

• Grade 2b: nerve conduction abnormality of stage 1a, a moderate degree of weakness (i.e., 50%) of ankle dorsiflexion with or without neuropathy symptoms.

ROLE OF VITAMIN B6 IN DIABETES

Vitamin B6 is a water-soluble vitamin and is metabolized and excreted fastly from the body thereby resulting in a very less toxicity. Vitamin B6 is a main compound for regulating the metabolizing of glucose, lipids, amino acids and various neurotransmitters[14]. There are mainly 6 common forms of vitaminB6 pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM) and 5' phosphate derivatives. The active form of vitamin B6 is pyridoxal 5'-phosphate which act as a coenzyme for more than 150 distinct enzymatic reactions of metabolism[15-17].

The microvascular hypothesis of Diabetic neuropathy states that high homocysteine, nitric acid and reduced levels of folic acid mainly occurs due to capillary membrane thickening and hypoxic changes and an important co factor for this metabolism is pyridoxine[18]. The recommended daily amount of dietary vitamin B6 is between 1.6-2mg/day for adults[19]. Vitamin B6 boosts the health of nerves and is essential in maintaining the proper functioning of nervous system. A deficiency in vitamin B6 can cause a stress in the nervous system and cause nerve damage.

Low level of pyridoxine can cause increase in homocysteine levels leading to damage inside the arteries[20]. In case of excessive oxidative stress there is increase in level of advanced glycated end products which is considered as one of the main reasons for developing DPN.Plasma pyridoxal 5'-phosphate concentration (PLP) is the best technique to measure the levels of vitamin B6.A person is said to have vitamin B6 deficiency if his/her PLP plasma concentration is lesser than 30nmol/L[21].

Most of the complications of diabetics occurs due to the formation of Advanced Glycated End products (AGEs). Glycating products also produces AGEs by reacting with amino acids of proteins. These AGEs will accumulate in the body and causes inflammation as well as destroy normal structure of blood vessels resulting in vascular problems[22,23].

Various studies shows that Vitamin B6 plays a major role in one of the AGE pathways by blocking 3-deoxyglucasone and thus preventing the binding to proteins[24].Studies also shows that vitamin B6 administration had significantly reduced neuropathy and also slowed the course of diabetic nephropathy. It is believed that the antioxidant properties of vitamin B6 has greater impact on diabetic problems[25,26].

DISCUSSION

The study reported that pyridoxine deficiency is prevalent among patients with diabetic neuropathy. About 51.8%of patients have vitamin B6 deficiency. There also exist a relationship that fasting blood sugar levels and glycated hemoglobin, pyridoxine deficiency can cause impaired glucose tolerance[27,28].

In the conversion of tryptophan to nicotinic acid pyridoxal 5'-phosphate act as a co enzyme. If this conversion is interrupted various intermediate products will be formed that have the potential to interact with biological insulin leading to insulin resistance[29]. The lower levels of viataminB6 in T2DM were thought to be because of poor reabsorption processes[30].

Various studies discovered that the plasma PLP levels in diabetic patients is significantly less when compared with healthy individuals[31].The decrease in the PLP levels could be because of an increase in demand by the PLP -dependent enzymes, immune cell proliferation or mobilization of the co enzyme the site of inflammation[32]. Our study shows that there is a direct significant relationship of pyridoxine and nerve conduction velocity. Also, pyridoxine cannot be synthesized by human on their own hence they are dependent on various sources for pyridoxine[33].

CONCLUSION

Vitamin B6 is a water-soluble vitamin whose deficiency can worsen diabetic complication. About 51.8%of patients with diabetes have vitamin B6 deficiency. There also exist a strong relationship between pyridoxine deficiency and glucose intolerance. Vitamin B6 supplements with its anti-oxidant properties are helpful in treating the symptoms of painful diabetic neuropathy.

ABBREVIATIONS

DM: Diabetes Mellitus

DPN: Diabetic Peripheral Neuropathy

PLP: Pyridoxal 5'-phosphate

AGE: Advanced Glycated End product

T2DM: Type 2 Diabetes Mellitus

FBS: Fasting Blood Sugar

DSPN: Diabetes Sensory Motor Neuropathy

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