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Original article

Impact of vitamin B6 deficiency on the severity of diabetic peripheral neuropathy – A cross sectional study

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ABSTRACT

Background: Diabetic Peripheral Neuropathy is one of the most important and significantly prevalent microvascular complications of Diabetes Mellitus. Pyridoxine is a key nutrient for protecting nerve health. The objective of this research is to study the prevalence rate of pyridoxine deficiency in Diabetic neuropathy patients, to understand the correlation between various biochemical and markers of diabetic neuropathy and pyridoxine deficiency.

Results: 249 patients were selected for the study based on the selection criteria participants. 51.8% prevalence of pyridoxine deficiency in Diabetic neuropathy patients. The nerve conduction velocity significantly reduced in pyridoxine deficiency cases ($p < 0.05$). A strong inverse relationship is observed with fasting blood sugar levels and glycated hemoglobin pyridoxine deficiency might contribute to impaired glucose tolerance.

Conclusion: There also exists a strong inverse relationship with glycemic markers. Significant direct correlation is observed with nerve conduction velocity. Pyridoxine also has properties of antioxidant which may be utilized for the management of Diabetic Neuropathy.

1. Background

Diabetic Neuropathy is one of the most important and significantly prevalent microvascular complications of Diabetes Mellitus (Chawla et al., 2016]. The microvascular hypothesis of Diabetic neuropathy postulates that it occurs due to capillary membrane thickening and hypoxic changes which may also lead to high homocysteine, nitric oxide and reduces folic acid. Pyridoxine is an important co-factor of this metabolism (Miranda et al., 2011].

The biologically active form of Vitamin B6 is pyridoxal 5′ phosphate (PLP) which is a co-factor for multiple enzymatic reactions and also a known antioxidant. One of the contributing factors for diabetic neuropathy is the advanced glycated end products which are predominantly higher in case of excessive oxidative stress. Pyridoxine deficiency might contribute to this pathway. Pyridoxine deficiency also directly leads to higher homocysteine levels by the impairment of enzymes such as cystathionine β- synthase (CBS) and cystathione γ- lyase (CGL) which all requires PLP as a co-enzyme (Kraus et al., 2009, Zhu et al., 2008).

There is a strong evidence linking vitamin B6 to diabetes and its side effects. PLP levels in diabetic groups and healthy participants have been compared in a few population screenings. Several studies have also focused on the effects of vitamin B6 on diabetes complications and the efficacy of vitamin B6 as a preventive measure. Plasma pyridoxal 5′-phosphate (PLP) concentration is a standard way to measure vitamin B6 levels, and a concentration below the threshold of 30 nmol/L is often indicative of insufficient vitamin B6 status. Measurements of plasma pyridoxal or total vitamin B6 and urinary 4-pyridoxic acid are other techniques (Plows et al., 2018).

Abbreviations: **DM**, Diabetes Mellitus; **FBS**, Fasting Blood Sugar; **BMI**, Body Mass Index; **IEC**, Institutional Ethics Committee; **MMA**, Methyl Malonic Acid; **SPSS**, Statistical Programme for social Sciences; **PLP**, Pyridoxal 5′ Phosphate; **CBS**, Cystathionine β- Synthase; **CGL**, Cystathione γ- Lyase; **ANOVA**, Analysis of Variance; **HbA1c**, Glycated Haemoglobin.

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Toyota *et al.* studyhas shown that pyridoxine shortage can affect insulin release in rats, revealed a cause-and-effect relationship between low PLP levels and diabetes (Toyota et al., 1981). Additionally, the authors discovered that insulin and glucagon secretion was compromised in pyridoxine depletion using in vitro pancreas perfusion tests.

Due to the fact that pyridoxine is transferred to the baby during pregnancy, PLP levels tend to fall, and because pyridoxine treatment improves glucose tolerance in GDM patients, it is thought that low vitamin B6 levels are the root cause of GDM (Bennink et al., 1975).

The production of AGEs is considered to be one of the primary causes of diabetes complications (Goldin et al, 2006). In diabetes, hyperglycemia leads to Advanced Glycation End products (AGE) buildup through a spontaneous chemical change in amine-containing molecules. Reducing sugars create adducts (Amadori products), such as glyoxal, methylglyoxal, and 3-deoxyglucosone, by covalently attaching free amino groups of proteins, lipids, and guanyl nucleotides in DNA (3-DG). In addition to being produced in Maillard reactions, these dicarbonyl molecules also result from lipid peroxidation, the polyol pathway, and glucose autoxidation processes (Marques et al., 2017). Glycating substances can produce more AGEs by reacting with proteins in turn since they are very reactive and powerful. It has been demonstrated that AGE accumulation results in inflammation and obliterates blood vessels' normal structure and function, creating vascular problems.

Low B6 levels have been linked in certain studies to diabetes problems in T1D and T2D patients, including neuropathy and retinopathy (Nix et al., 2015). While previous studies have shown that vitamin B6 administration significantly decreased neuropathy (Cohen et al., 1984) and slowed the course of diabetic nephropathy. It is believed that vitamin B6′s function as an antioxidant molecule has the greatest impact on diabetes problems.

It was suggested that PLP might trap 3-DG, one of the AGE pathway products, in order to explain how vitamin B6 prevents AGE production (Marques et al., 2017). In vitro tests revealed that PL and PM were less reactive than PLP, which significantly reduced 3-DG levels in a dose-dependent manner (Kluger et al., 2008). Serum homocysteine is a marker for neuropathy, studies have shown deficient pyridoxine levels leads to hyperhomocystenemia. Methyl Malonic Acid is a marker for neuropathy. C reactive protein is an acute phase biomarker of inflammation. Nerve conduction velocity is used to assess neuropathy.

The objective of this research is to study the prevalence rate of pyridoxine deficiency in Diabetic neuropathy patients, to understand the correlation between various biochemical and markers of diabetic neuropathy and pyridoxine deficiency.

2. Methods

2.1. Study design

A prospective cross-sectional study was carried out in the general medicine department at a tertiary care teaching hospital during the period January 2022 to November 2022. Sample size was estimated using the prevalence data of total diabetic peripheral neuropathy patients and it was derived to be 249. All the study participants provided a written informed consent to participate in the study.The Study was approved by the Institutional ethics committee with the approval number St.Peter's IEC/2021/II/09.

2.2. Patient eligibility and exclusion criteria

Patients above 18 years of age who are clinically confirmed with Diabetic Neuropathy, diagnosed with Diabetes Mellitus in<5 years are only included. Patients with Fasting Blood glucose levels in the range of 126–250 mg/dl and HbA1c levels in the range of 7–9% are included in the study since higher glucose levels require multiple drug regimen and receiving only Metformin and Pregabalin medications are taken into the study.. Patients with long term Diabetes Mellitus with Fasting Blood sugar levels above 250 mg/dl and HbA1C levels above 9% are excluded from the study, who did not provide consent for the study receiving other Hypoglycemic drugs except Metformin and with serum creatinine levels>1.5 mg/dl are all excluded. Patients with Epilepsy, Tuberculosis, Dyslipidemia, thromboembolism, Inflammatory Bowel Disease, Bowel Resection surgery, Adrenal Insufficiency are also excluded from the study (Basura et al.,2009, Levin et al.,1981).

The data was collected from the patients with the help of data extraction form to obtain preliminary data regarding the age, sex, and family history of Diabetes Mellitus, and other parameters such as smoking history, Alcoholism, duration of diabetes, past medical history etc. Body Mass Index (BMI) of patients was also calculated and included. Glycemic status parameters such as fasting blood glucose (FBS) and G = glycated haemoglobin (HbA1C) were recorded using conventional methods.

The patients were categorized into three groups depending upon their serum Vitamin B6 levels such as Sufficient (serum Vitamin B6 > 5 μg/L), Insufficient (serum Vitamin B6 3 μg/L to 5 μg/L) and Deficient (serum Vitamin B6 < 3 μg/L).

2.3. Statistical analysis

Descriptive statistics were used to analyze the preliminary data in the form of Mean ± SEM. The baseline parameters were analyzed using one-way ANOVA and Chi-squared tests as appropriate with a significance level of 95%. Pearson correlation was used to correlate the association between each variable in a cohort with serum Pyridoxine levels. All the univariate analyses used a $p < 0.05$ to be considered statistically significant. The statistical analyses were carried out using IBM SPSS (Statistical Programme for social Sciences version 22) and Graphpad prism version 9.0.

3. Results

Initially, 372 patients were screened and 249 patients were included in the study based on the inclusion criteria. Patients' family history, social habits and the duration of diseases are provided under Table 1.

Table 1
Baseline characteristics.

Parameters	Sufficient (serum Vitamin B6 > 5 μg/L)	Insufficient (serum Vitamin B6 3 μg/L to 5 μg/L)	Deficient (serum Vitamin B6 < 3 μg/L)
No. of Patients n(%)	48 (19.27)	72 (28.91)	129 (51.80)*
Age in yrs	47.16 ± 3.26	44.6 ± 3.24	42.6 ± 3.12
Male n (%)	24 (9.63)	45 (18.07)	72 (28.91)
Family History n(%)	27 (10.84)	24 (9.63)	60 (24.09)
Smoking	18 (37.5)	30 (41.67)	36 (27.91)
Current			
Past	09 (18.75)	18 (25.00)	21 (16.28)
Non-Smokers	21 (43.75)	34 (47.22)	72 (55.81)
Duration of Diabetes Mellitus in yrs	2.6 ± 0.4	3.2 ± 0.6	3.1 ± 0.94
Duration of Diabetic Peripheral Neuropathy in yrs	0.8 ± 0.2	1.1 ± 0.3	0.9 ± 0.6

All values are mentioned as mean ± SEM unless stated otherwise. * denotes $p < 0.05$ on performing chi squared analysis.

Results show that 51.8% prevalence of pyridoxine deficiency in Diabetic neuropathy patients [Table 1]. Subsequently only 19.27% of the diabetics had a sufficient amount of serum pyridoxine levels indicating a strong evidence of reduced vitamin B6 levels.

In addition, nerve conduction velocity significantly reduced in pyridoxine deficiency including insufficient level cases [Table 2]. Further,glycemic parameters as well as acute inflammatory markers have greatly varied in deficient patients [Table 3].Table 4.

Serum homocysteine andglycemic markers have a significant inverse correlation whereas nerve conduction velocity has extremely significant Direct relationship [Table.3].

4. Discussion

Our study reported that pyridoxine deficiency is prevalent among diabetic neuropathy patients (51.8%) which contradicts the report published by Levin ER *et al.* (Levin et al.,1981). The study by Levin ER et al claimed only 1 out of 18 patients had deficient status. Our study claimed 51.8% deficiency. Our study has a larger population size and similar to the results produced by Nix W A et al. (Nix, 2015) on Diabetic Nephropathy where the prevalence of B6 deficiency is 63% and 58% with and without microalbuminuria respectively.

In our study we found that a strong inverse relationship is observed with fasting blood sugar levels and glycated hemoglobin pyridoxine deficiency might contribute to impaired glucose tolerance (Oxen et al., 2013). Pyridoxal 5 phosphate is an important co-factor in the conversion of tryptophan to nicotinic acid. If this pathway does not work properly various intermediate metabolites will be produced. These intermediate metabolites interact with biological insulin leading to an increased insulin resistance thus contributing to impaired glucose tolerance (Morino-Navarrete et al., 2016, Liu et al. ,2016).

The results of a study conducted in Korea by Ahn *et al.* (Ahn et al., 2011) and a study conducted in Germany by Nix *et al* (Nix, 2015) revealed an apparent inverse relationship between vitamin B6 levels and the development of diabetes. The diabetic group examined by Nix (Nix, 2015), which was made up of individuals with advanced clinical stage, displayed median plasma concentrations of PLP were significantly decreased in a diabetic group compared to the controls. In contrast, Ahn et al. (Ahn et al., 2011) examined diabetic individuals with an early status of the disease and found a mean plasma PLP level reduction to be relevant but not statistically significant, with respect to controls. Lowered vitamin B6 levels in T2D patients were thought to be caused by poor reabsorption processes (Iwakawa et al., 2016).

In a cross-sectional case-control research, Satyanarayana et al. (Satyanarayana et al., 2011) discovered that the mean plasma PLP levels in T2D participants were considerably lower than the healthy controls.As a result, it was suggested that the decrease in PLP levels in diabetes could be attributed to the following reasons like an increase in demand by the PLP-dependent enzymes involved in the tryptophan kynurenine pathway, immune cell proliferation and the mobilization of this coenzyme to the site of inflammation (Paul et al., 2013). To validate these pathways, more studies are necessary.

In our study, pyridoxine had a direct extremely significant relationship with nerve conduction velocity. Pyridoxine cannot be synthesized by human on their own, hence they depend upon the natural sources to get the required levels of pyridoxine (Parra et al., 2018). The limitation of this study was that it is selected from a single geographical location. In future, a large cross-sectional studies may be carried out to confirm the role of pyridoxine deficiency in Diabetic neuropathy. Studies can be carried out with patients using multiple oral hypoglycemic agents and also the effectiveness of supplementing pyridoxine may be studied in the future.

Table 2
Glycemic Status, Biochemical Markers and Neuropathy Markers.

Parameters	Sufficient	Insufficient	Deficient
Fasting Blood sugar mg/dL	162.6 ± 3.2	171.4 ± 3.9	189.6 ± 2.6*
HbA1c (%)	7.3 ± 0.6	7.9 ± 0.4	8.6 ± 0.3*
Serum Homocysteine	12.9 ± 0.6	13.1 ± 0.7	15.6 ± 0.4*
Methyl Malonic Acid	0.64 ± 0.3	0.53 ± 0.2	0.62 ± 0.42
C Reactive Protein	2.6 ± 0.9	3.4 ± 0.5	3.9 ± 0.6*
Nerve Conduction Velocity m/s	39.6 ± 0.4	34.2 ± 0.6*	29.6 ± 0.4*
Mono Filament Test	3.61 ± 0.64	4.24 ± 0.21	5.96 ± 0.21*

All values are mentioned as mean ± SEM unless stated otherwise. * denotes p < 0.05 on performing ANOVA followed by a post hoc analysis.

Table 3
Correlation of variables with Pyridoxine levels:

Parameters	Mean ± SEM	p value	r value
Fasting Blood sugar	179.6 ± 3.2	0.0052	−0.7951*
HbA1c	8.1 ± 0.6	0.0069	−0.7141*
Homocysteine	14.6 ± 0.6	0.0021	−0.7966*
Methyl Malonic Acid	0.5 ± 0.32	0.0984	0.1621
C Reactive Protein	3.5 ± 0.4	0.0514	−0.6041
Nerve Conduction Velocity m/s	32.6 ± 1.6	<0.0001	0.9142**
Mono Filament Test	4.56 ± 0.8	0.0061	−0.8021*
BMI	25.2 ± 0.6	0.0572	0.5521
Serum Pyridoxine	3.1 ± 0.6	NA	1

All values are mentioned as mean ± SEM unless stated otherwise. * denotes p < 0.05 and ** denotes p < 0.001 on performing the 2 tailed pearson correlation.

Table 4
Linear Regression Analysis of Variables:

Parameters	R	r^2	P
Fasting Blood sugar	−0.7951	0.6321	0.0052*
HbA1c	−0.7141	0.5099	0.0069*
Homocysteine	−0.0410	0.0016	0.0721
BMI	0.5521	0.3048	0.0572
Age	0.5601	0.3137	0.0624
Nerve Conduction Velocity m/s	0.9142	0.8357	<0.0001**

*P < 0.05 is considered significant. **P < 0.001 is considered extremely significant.

5. Conclusion

There is a 51.8% prevalence of pyridoxine deficiency among diabetic neuropathy patients. There also exists a strong inverse relationship with glycemic markers. Significant direct correlation is observed with nerve conduction velocity. Pyridoxine also has properties of antioxidant which may be utilized for the management of Diabetic Neuropathy.

Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: MK, GK, RV,PK,SP,PD,RCP; data collection: PD,RCP; analysis and interpretation of results: MK,GK,RV,PK,SP,PD,RCP,RD,MN,AA; draft manuscript preparation: MK,GK,RV,PK,SP,PD,RCP,RD,MN,AA. All authors reviewed the results and approved the final version of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

The study was approved by the institutional ethics committee St.Peter's IEC/2022/14. All the study participants have provided a written informed consent for their willingness to participate in this study.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

References:

Ahn, H.J., Min, K.W., Cho, Y.O., 2011. Assessment of vitamin B(6) status in Korean patients with newly diagnosed type 2 diabetes. Nutr. Res. Pract. 5, 34–39. https://doi.org/10.4162/nrp.2011.5.1.34.

Basura, G.J., Hagland, S.P., Wiltse, A.M., Gospe, S.M., 2009. Jr Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry. Eur. J. Pediatr. 168, 697–704.

Bennink, H.J., Schreurs, W.H., 1975. Improvement of oral glucose tolerance in gestational diabetes by pyridoxine. Br. Med. J. 3, 13–15. https://doi.org/10.1136/bmj.3.5974.13.

Chawla, R., Chawla, A., Jaggi, S., 2016. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J. Endocrinol. Metab. 20 (4), 546.

Cohen, K.L., Gorecki, G.A., Silverstein, S.B., Ebersole, J.S., Solomon, L.R., 1984. Effect of pyridoxine (vitamin B6) on diabetic patients with peripheral neuropathy. J. Am. Podiatry Assoc. 74, 394–397. https://doi.org/10.7547/87507315-74-8-394.

Goldin, A., Beckman, J.A., Schmidt, A.M., Creager, M.A., 2006. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation. 114, 597–605.

Iwakawa, H., Nakamura, Y., Fukui, T., Fukuwatari, T., Ugi, S., Maegawa, H., Doi, Y., Shibata, K., 2016. Concentrations of water-soluble vitamins in blood and urinary excretion in patients with diabetes mellitus. Nutr. Metab. Insights. 9, 85–92.

Kluger, G., Blank, R., Paul, K., Paschke, E., Jansen, E., Jakobs, C., Wörle, H., Plecko, B., 2008. Pyridoxine-dependent epilepsy: normal outcome in a patient with late diagnosis after prolonged status epilepticus causing cortical blindness. Neuropediatrics 39, 276–279.

Kraus, J.P., Hasek, J., Kozich, V., Collard, R., Venezia, S., Janosikova, B., Wang, J., Stabler, S.P., Allen, R.H., Jakobs, C., Finn, C.T., Chien, Y.H., Hwu, W.L., Hegele, R.A., Mudd, S.H., 2009. Cystathionine gamma-lyase: clinical, metabolic, genetic, and structural studies. Mol. Genet. Metab. 97, 250–259.

Levin, E., Hanscom, T., Fisher, M., Lauvstad, W., Lui, A., Ryan, A., et al., 1981. The influence of pyridoxine in diabetic peripheral neuropathy. Diabetes Care. 4 (6), 606–609.

Liu, Z., Li, P., Zhao, Z.H., Zhang, Y., Ma, Z.M., Wang, S.X., 2016. Vitamin B6 prevents endothelial dysfunction, insulin resistance, and hepatic lipid accumulation in apoe (-/-) mice fed with high-fat diet. J. Diabetes Res. 2016, 1748065. https://doi.org/10.1155/2016/1748065.

Marques, C.M.S., Nunes, E.A., Lago, L., Pedron, C.N., Manieri, T.M., Sato, R.H., Oliveira, V.X.J., Cerchiaro, G., 2017. Generation of Advanced Glycation End-Products (AGEs) by glycoxidation mediated by copper and ROS in a human serum albumin (HSA) model peptide: Reaction mechanism and damage in motor neuron cells. Mutat. Res. 824, 42–51.

Miranda-Massari, R., Gonzalez, M.J., Jimenez, F.J., Allende-Vigo, Z.M., Duconge, J., 2011. Metabolic correction in the management of diabetic peripheral neuropathy: improving clinical results beyond symptom control. Curr. Clin. Pharmacol. 6 (4), 260–273.

Moreno-Navarrete, J.M., Jove, M., Ortega, F., Xifra, G., Ricart, W., Obis, E., et al., 2016. Metabolomics uncovers the role of adipose tissue PDXK in adipogenesis and systemic insulin sensitivity. Diabetologia 59, 822–832. https://doi.org/10.1007/s00125-016-3863-1.

Nix, W.A., Zirwes, R., Bangert, V., Kaiser, R.P., Schilling, M., Hostalek, U., Obeid, R., 2015. Vitamin B status in patients with type 2 diabetes mellitus with and without incipient nephropathy. Diabetes Res. Clin. Pract. 107, 157–165. https://doi.org/10.1016/j.diabres.2014.09.058.

Oxenkrug, G., 2013. Insulin resistance and dysregulation of tryptophan-kynurenine and kynurenine-nicotinamide adenine dinucleotide metabolic pathways. Mol. Neurobiol. 48, 294–301. https://doi.org/10.1007/s12035-013-8497-4.

Parra, M., Stahl, S., Hellmann, H., 2018. Vitamin B6 and Its Role in Cell Metabolism and Physiology. Cells. 7 (7), 84.

Paul, L., Ueland, P.M., Selhub, J., 2013. Mechanistic perspective on the relationship between pyridoxal 5′-phosphate and inflammation. Nutr. Rev. 71, 239–244.

Plows, J.F., Stanley, J.L., Baker, P.N., Reynolds, C.M., Vickers, M.H., 2018. The Pathophysiology of Gestational Diabetes Mellitus. Int. J. Mol. Sci. 19, 3342. https://doi.org/10.3390/ijms19113342.

Satyanarayana, A., Balakrishna, N., Pitla, S., Reddy, P.Y., Mudili, S., Lopamudra, P., Suryanarayana, P., Viswanath, K., Ayyagari, R., Reddy, G.B., 2011. Status of B-vitamins and homocysteine in diabetic retinopathy: Association with vitamin-B12 deficiency and hyperhomocysteinemia. PLoS ONE. 6, e26747.

Toyota, T., Kai, Y., Kakizaki, M., Ohtsuka, H., Shibata, Y., Goto, Y., 1981. The endocrine pancreas in pyridoxine deficient rats. Tohoku J. Exp. Med. 134, 331–336. https://doi.org/10.1620/tjem.134.331.

Zhu, W., Lin, A., Banerjee, R., 2008. Kinetic properties of polymorphic variants and pathogenic mutants in human cystathionine gamma-lyase. Biochemistry. 47, 6226–6232.