Int J Pharm Bio Sci 2014 July ; 5 (3) : (B) 647 - 652

Research Article **Biochemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

SIGNIFICANCE OF VITAMIN B12 DEFICIENCY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Nutritional deficiency of B12 is very common in pure vegetarians. Vegetarians suffering from type 2 Diabetes Mellitus and metformin treatment are predisposed to vitamin B12 deficiency and hence diabetic neuropathy and diabetic foot. We estimated B12 levels in patients with type 2 Diabetes Mellitus who are pure vegetarians on metformin therapy (cases), normal healthy individuals (controls). We found that B12 levels are significantly low in type 2 Diabetes Mellitus group when compared to control group with $P<0.001$ and 95% confidence intervals for mean being 201.65-227.60 and 583.90-802.88 in type 2 Diabetes Mellitus and controls respectively. Hence B12 estimation is necessary to identify B12 deficient patients. From several previous studies, we suggest that parenteral supplementation of vitamin B12 may help to prevent neuropathy, and diabetic foot in type 2 Diabetes Mellitus patients on metformin therapy. Clinical trials are required to establish the mode of supplementation of vitamin B12 for optimum clinical utility.

KEYWORDS: Vitamin B12 deficiency, type 2 Diabetes Mellitus, diabetic neuropathy, supplementation.

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INTRODUCTION

The world Health Organisation estimates that type 2 diabetes mellitus (T2DM) afflicts ~200 million people worldwide and its prevalence will nearly double within 30 years.(21) Universally, there has been an understanding that diet is the integral part of modalities of treatment in diabetes. However, people with diabetes will have different responses to particular foods because of their different genes.(21) Incidence of type 2 DM is to increase in urban population as well as rural population. Urbanisation has brought a change in life style. Increased stress and change in food habits contribute to the increased occurrence of type 2 DM, hence determining comorbid factors that are associated with diabetic complications such as diabetic polyneuropathy and diabetic foot is highly important. In type 2 DM, B12 deficiency, (severe and borderline) manifests as neuropathy. The symptoms of diabetic neuropathy over lap with impaired neurocognitive manifestations with B12 deficiency (3, 4). Thus, identifying the correct reason for the development of this complications which are observed in diabetic neuropathy such as paresthesias impaired vibration sense and impaired proprioception is crucial. Simple measure of supplementating vitamin B12 may reverse neurological symptoms in metformin treated type 2 DM patients who are vegetarians, there by helps in preventing severe neuropathy complications such as diabetic foot. Vitamin B12 is present in foods of animal origin only, and is not present in foods of vegetable sources. Thus vegetarians are at increased risk for vitamin B12 deficiency. Vitamin B12 deficiency is associated with hematological and neurological features. Hematological changes are macrocytic anaemia, low RBC count and Hb content. Other changes that occur due to vitamin B12 deficiency are mucosal atrophy of stomach, pharynx, achlorhydria. Neurological features incude, degenerative changes of the posterior and lateral columns of spinal cord resulting in sensory disturbances, hyperactive reflexes, and paralysis. Biochemically vitamin B12 deficiency causes increased homocysteine levels in blood which itself is a well known risk factor for cardiovascular diseases. Metformin is the first line drug of choice to lower blood glucose levels along with lifestyle modifications. Its efficacy has been proved by several studies(7,8). Despite its high efficacy to lower blood glucose level it has been found decrease vitamin B12 levels(2,9,10,11,12). The risk of developing metformin associated B12 deficiency increases with age and duration of treatment(12) and in vegetarians(6). Metformin has been shown to inhibit vitamin B12 by altering the small bowl motility which leads to bacterial growth and vitamin B12 deficiency. Other mechanisms include alterations in intrinsic factor (IF) levels due to decreased secretion of intrinsic factor and interaction with cubulin endocytic receptor(14). In addition to these mechanisms it also has been shown to inhibit the calcium dependent absorption of the vitamin B12-IF complex at the terminal ileum(18). Decrease in vitamin B12 absorption following metformin use typically starts as early as the fourth month(5). Clinically overt features of vitamin B12 deficiency manifests by 5-10 years owing to the large body stores in the liver mainly that are not quickly depleted. Hence the basis of our study is to detect a vitamin B12 deficiency in type 2 diabetic patients who are strict vegetarians. vegetarianism is associated with vitamin B12 deficiency superimposed with metformin therapy for type 2 diabetic patients, that becomes an important factor in the early development of diabetic neuropathy and diabetic foot.

MATERIALS & METHODS

This study used a cross sectional design to estimate the significance of vitamin B12 deficiency in 89 patients both male and female with type 2 diabetes in the age group of 35-70 years and 89 age matched normal healthy individuals as a control group. Selection of patients was done based on existing type 2 Diabetes Mellitus individuals already on treatment with metformin, who are

vegetarians. Hence inclusion criteria are type 2 diabetes mellitus patients in the age group of 35-70 years, vegetarians on metformin therapy. Exclusion criteria are multivitamin supplementation.

LABORATORY INVESTIGATIONS

Vitamin B12 levels are estimated by chemiluminiscence technique on Advia Centour CP analyzer. Vitamin B12 levels <150 pg/ml are taken as deficient, and vitamin B12 levels > 150 to 300 pg/ml are taken as border line. To confirm the B12 deficiency in border line group the specimens were analysed for homocystine levels. Specimens with homocystine levels above the upper limit of reference interval were considered elevated which is indicative of vitamin B12 deficiency.

RESULTS

Results have been analysed by using student T test (2-tail) with (α=5%) with 95% confidence intervals. There is a Significant difference between the groups ($p<0.001$) cases and controls. The following figure 1 clearly depicts the difference between cases and control group. The statistical tables show the mean SD (Table-1) and 95% CI intervals for cases and controls. Table-2 indicates student T-test with $p<0.001$ which is highly significant.

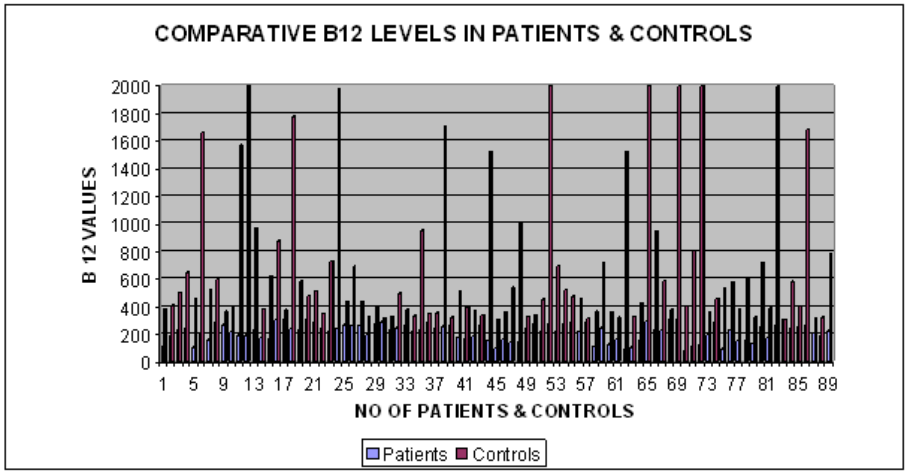

Figure-1
Bar diagram depicting levels of B12 in cases and controls Means Descriptives B 12

Table-1
Mean and SD and 95% CI values of B12 in (1-Controls), (2-Cases)

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
1	89	693.39	519.770	55.096	583.90	802.88	306	2000
2	89	214.63	61.592	6.529	201.65	227.60	81	306

Independent Samples Test

Table-2
Independent sample test, showing to tailed T-test with significance <.000

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	
B 12	Equal variances assumed	84.848	.000	8.629	176	.000	478.764	55.481	369.270	588.258
	Equal variances not assumed			8.629	90.471	.000	478.764	55.481	368.549	588.979

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of log is the same across categories of group.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.

Figure-2
Null hypothesis showing significance <.000
Significant different between the group (p<0.001)

DISCUSSION

Our results show clear a difference between cases and controls with mean values of 214.63 and 693.39 respectively (Table-1) student T-test gives significance difference between cases and controls with p<0.001 which is highly significant (Table-2) null hypothesis is rejected (Figure-2) Type 2 diabetes is common in above 40 years age the age limit comes done with modernization and urbanization. In India, a country with a large proportion of vegetarians due to cultural and religious believes very high prevalence of vitamin B12 deficiency among the general population has been reported[1]. Yajnik et al determine vitamin B12 deficiency and hyper homocystinemia among 441 healthy middle aged Indian men, 67% of the study participants reported vitamin B12 deficiency as defined by vitamin B12 concentrations <150 pmol/l[6]. Vegetarian diet was the soul significant factor associated with low vitamin B12 levels in the study. In the absence of contraindication like renal and hepatic dysfunction recent guidelines advocate for the use of metformin as the first line glucose lowering agent[7,8]. Despite its very superior glycemic lowering effect, metformin has for long been shown to decrease vitamin B12 levels. The studies performed by DeFronzo et al[2], Hermann L et al[9], Nervo M et al[10], Kos E et al[11], Dejager J et al[12], Bell D et al[13], have demonstrated the side effect of metformin in decreasing vitamin B12 levels and the duration of treatment is also associated with vitamin B12 deficiency[12]. Despite the high prevalence of B12 deficiency in general and diabetic population effect of it in causing diabetic neuropathy and diabetic foot insome individuals is unknown. As per national diabetes fact sheet, United States of America 60-70% of diabetic patients have mild to severe forms of nervous system damage[15]. The most common manifestation is peripheral neuropathy. In India, a country with a large number of vegetarians owing to religious and cultural beliefs prevalence of B12 deficiency is very high. Strong association between the diabetic neuropathy and B12 deficiency can be attributed to both dietary and therapeutic factors. Previous studies have demonstrated that supplemental vitamin B12 improves

somatic and autonomic symptoms of diabetic neuropathy[16,17]. Testing for and treating B12 deficiency in patients with neuropathy may lead to improved clinical outcomes and prevent development of diabetic foot. Identification of patients with B12 levels <300pg/ml may help the clinician to look for more specific markers to establish the diagnosis. Whether vitamin B12 deficiency in type2 DM is due to vegetarianism or due to drugs vitamin replacement therapy should be done. Oral supplementation in type 2 DM patients on long term therapy with metformin is ineffective in treating B12 deficiency(19). B12 deficiency, hyperhomocysteinemia may reduce the quality of life of a di people with diabetesabetic patient. Clinical trials are required to establish the efficacy of parenteral B12 supplementation to reverse symptoms diabetic neuropathy, and whether it helps in the faster recovery from diabetic foot which is very common complication of diabetes in urban and rural population.

CONCLUSION

Our results established strong correlation of low and borderline levels of vitamin B12 with diabetic neuropathy i.e. P<0.001. Type 2 diabetic patients on treatment with metformin and pure vegetarians have significantly low B12 levels compared to normal healthy individuals. B12 deficiency in vegetarians with type 2 DM on metformin therapy is to be considered as a comorbid factor which can lead to worsening of diabetic neuropathy and hence diabetic complications particularly diabetic foot. Detection of B12 deficiency in all vegetarian type 2 Diabetic patients on treatment with metformin is necessary to prevent neural damage and to do early intervention to reverse the deficiency status. Supplementation of vitamin B12 may be mandatory. Clinical trials are needed to evaluate the dosages and mode of admission (Parenteral) of B12 to affected patients.

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