Original Research

To Study The Level Of Vitamin B12 And Its Association With Hba1c In Diabetes Patients

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ABSTRACT:

Introduction- Vitamin B12, an essential micronutrient which is required for optimal hemopoetic, neuro- cognitive and cardiovascular function. High prevalence of Biochemical and clinical vitamin B12 deficiency have been demonstrated with diabetes mellitus. It presents with wide range of clinical manifestations from megaloblastic anaemia pancytopenia impaired memory, dementia, delirium, peripheral neuropathy, sub- acute combined degeneration of the spinal cord. Increased frequency of vitamin B12 deficiency among the diabetic patients has been documented in several cross sectional studies and case reports. The prime factor associated with vitamin B12 deficiency among patients with DM is Metformin use. **Objectives-**To study the level of Vitamin B12 in diabetic patients and its association with HbA1c and correlation of vit.b12 deficiency with antidiabetic drug metformin. **Methods**-This study was conducted in Department Of Medicine, L.L.R.M Medical College, Meerut. People from medicine OPD/IPD were selected .A total of 180 prediagnosed cases of DM which were already on antidiabetic treatment (metformin, insulin therapy and other OHAs)were enrolled in this study. **Results-**In this cross sectional study, 180 DM patients were enrolled and they were divided in two groups those who are taking metformin (group A) where as patients on insulin and other oral hypoglycaemic agents are placed in group B.The cases on metformin had the prevalence of vitaminB12 deficiency is 16.6% which is significance on regards to another group. It is also dependant on the dose and the duration of drug and the duration of disease. But in the groupB the deficiency prevalence is7.6% ,In this among the group B had 6 thelow vitamin level and 18 had normal level 66 had high level which comes in the following % respectively7.6,21.4 &69.8where as in cases it is16.5 42.6, 34.6 so metformin group had noticeable vitaminB12deficiency prevalence comparing to group B. When study participants were analyzed for intergroup differences in B12 levels, the mean difference in B12 levels between GroupB (Insulin+ non biguanide OHA) and GroupA (Metformin) group was 356.70mcg/dl, and when independent t- test was applied, highly statistical significant values with p values <.001 was obtained. **Conclusion-**This cross-sectional comparative study concludes that the persons with DM on chronic metformin therapy showed lower levels of serum vitamin B12 status compared to persons not treated with metformin. This represented that metformin takes a possible risk for vitamin B12 deficiency. This study suggest vit B12 deficiency not associated with HbA1c, Vit. B12 deficiency in Diabetes patients significantly associated with dose and duration of metformin therapy. It also recommend vitamins screening if therapy is advised for prolonged periods to avoid the neuropathic complication which are more common in diabetics due to the advanced glycation end products.

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INTRODUCTION

A vitamin B12 deficiency is a serious disorder, but it is never just a B12 deficiency because vitamin and mineral deficiencies never happen in isolation. Patients have type 2 diabetes, have chances of developing vitamin B12 deficiency are greater than those of non-diabetics. That's because metformin, a popular drug for diabetes interferes with vitamin B12 absorption, causing severe B12 deficiency.Those with type 1 diabetes are at a higher risk for other autoimmune disorders such as Coeliac disease or thyroid problems. They are also at higher risk of

developing pernicious anaemia, a condition where antibodies are produces against the carrier of vitamin B12 in the gut, *intrinsic factor*. This increase the likelihood of B12 deficiency as vitamin B12 is not protected as it passes through the gut. In type 2 diabetes, metformin therapy is associated with B12 deficiency, resulting in a 10% higher risk of developing B12 depletion. Metformin use and risk of B12 deficiency increases with the dose and the duration. Reduced absorption of vitamin B12 is a side effect of long-term use of metformin. Some studies have shown that metformin can reduce the absorption of vitamin B12 in 30% of people with type 2 diabetes (Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy) Hemoglobin A1c (HbA1c), also known as glycated hemoglobin can be used as an indicator of a patient's glycemic status for over a previous 3 months (Telen et al., 2004). Any condition that shorten the life span of erythrocytes is likely decrease the HbA1c level. Iron and Vitamin B12 deficiency renal failure and bone marrow suppression in alcoholism inhibit erythropoiesis and increase the mean survival of erythrocyte leading to increase HbA1c level; However hemolytic anemia, chronic liver disease and increase hemolysis from spleenomegally increase reticulocyte and decrease the mean age of erythrocyte which can decrease HbA1c level. Since Vitamin B12 deficiency affects erythropoiesis and is itself cause of anemia it is likely that HbA1c level will be affected in Vitamin B12 deficiency anemia.

MATERIAL AND METHODOLOGY

The work was conducted in Department Of Medicine, L.L.R.M Medical College, Meerut. People from medicine OPD/IPD were selected. A total of 180 patients were enrolled in this study.

METHOD OF COLLECTION OF DATA

Study will be include diagnosed Diabetic (Type-I, Type-II) patient of both sexes.

All patients will be interviewed and detailed history will be taken regarding type of diabetic mellitus and duration of diabetes mellitus, personal history including smoking and alcohol intake, clinically examined detailed physical examination will be done, informed consent will be obtained from all patients for study. Patients confidentially will be maintained.

INCLUSION CRITERION

The inclusion criteria of the study were
1. Diagnosed diabetic patients.
2. Patient already on antidiabetic treatment.
3. 30-80 years of age, both gender regardless on treatment and their glycemic status.

EXCLUSION CRITERION

- CKD with creatinine >3mg/dl.
- Prior bariatric surgery, gastrostomy, ileum resection
- Patient on orally B12 supplementation in last 6 months
- Patient have malabsorption disease (Crohan's disease)
- Patient of acute and chronic blood loss, hemolytic anemia.
- Pregnancy
- Chronic liver disease
- Alcoholics
- Rheumatoid arthritis
- Patient of pernicious anemia/Folate deficiency anemia due to chronic disorder.
- Drug such as ART and Ribavirine and Dapsone

STUDY DESIGN

Cross sectional study

OBSERVATIONS AND RESULTS

Table 1: Duration of Diabetes among study groups A (metformin) and Group B (non-metformin) in DM.

	Group	N	Mean In Years	Std. Deviation	Std. Error Mean	P value
Duration of DM	A	90	5.1333	4.27253	.63691	.632
	B	90	5.5111	3.08679	.46015	

In above table mean duration of diabetes in group A was 5.133 years and group B was 5.55 years which was No statistical significance was obtained with regards to duration of diabetes pharmacotherapy between groups.

Table 2: Comparison HBA 1C level in both group A (on metformin) and group (non-metformin) in diabetes patients in our study

	Group	N	Mean	Std. Deviation	P Value
	A	90	8.000	.3619	.014
HbA1C	B	90	7.996	.2618	Not significant

Among the group A, the mean HBa1c was 8.00. The mean HBa1c in Group B was 7.996. P value (0.014 was not statistically significant).

Table 3: Variation of HbA1c and vitamin b12 level in Group A (on metformin) and Group B(non-metformin) in Diabetes Mellitus Patient.

					Vitamin B12 level		
			HB1AC	No. of Patients	Deficient	Borderline	Normal
Group A			6.5-7.5	28	4	8	16

		HB1AC	No. of Patients	Deficient	Borderline	Normal
	Type-2 Diabetics on metformin	7.6-8.5	36	6	12	18
		8.6-9.5	20	5	8	7
		>9.5	6	3	2	1
	Total		90	18	30	42

					Vitamin B12 level		
			HB1AC	No. of Patients	Deficient	Borderline	Normal
Group B	Type-2 Diabetics non -metformin group		6.5-7.5	25	0	4	21
			7.6-8.5	33	2	7	24
			8.6-9.5	14	1	2	11
			>9.5	4	1	1	2
	Type 1 Diabetics Non-metformin group		6.5-7.5	0	0	0	0
			7.6-8.5	3	0	1	2
			8.6-9.5	5	1	1	3
			>9.5	6	2	2	2
	Total			90	7	18	65

Table 4: Comparison of percentage of vitamin B12 deficient & borderline deficient of Group A (Metformin)& B (Non-Metformin) in Diabetes Mellitus Patients

Groups	Deficient (No. of Patients in %)	BorderlineDeficient (No. of Patients in %)	Normal(No. of Patients in %)	Total (No. of Patients in %)	χ^2 Statistics	P Value
A Metformin	20%	33.33%	46.66%	100%		
B Non- Metformin	7.7%	20%	72.3%	100%	12.78	.005**

** highly statistically **si**gnificant
In the above table Group A (on Metformin) had 20% Deficient, 33.33% Borderline, 46.66% Normal patient in compare to Group B (Non-Metformin) 7.7% Deficient, 20% Borderline, 72.3% Normal, group A statistically significantly associated with vita b12 deficiency with group , P-value -.005

Table 5: Comparison of mean of Vitamin B12 levels between Group A (on Metformin) & Group B (Non-Metformin) in Diabetes Mellitus Patients

Group	N	Mean Vita B12level mcg/dl	Std. Deviation	. Errormean	P value
A (on metformin)	90	754.504	395.7267	58.9915	<.001**
B (non- metformin)	90	1111.202	414.7199	61.8228	Highly significant

In among table mean B12 level of group A (on metformin) was 754.504 mcg/dl and Group B (non- metformin) was 1111.2. When study participants were analyzed for intergroup differences in B12 levels, the mean difference in B12 levels between GroupB (non-metformin) and Group A (Metformin) group was 356.70mcg/dl, and when independent t- test was applied, highly statistical significant values with p values <.001 wasobtained.

Table 6: Comparison of the Dietary Habit of Group A (on Metformin) & Group B (Non-Metformin)

Groups	No. of Vegetarian Patients	No. of Mix (Veg& Non-Veg) Patients	Total	χ^2	P Value
A (on Metformin)	35 (38.88%)	55 (61.11%)	90		
B (Non-Metformin)	40 (44.44%)	50 (55.55%)	90	.57	.449**

** Statistically not significant
Above table show the comparison of the Group A (on Metformin) with Group B (Non-Metformin) notstatistically significant inter group variation exist with regards dietary habits

Table 7: Variation of GBP feature in Vit. B12 Deficient Patient in Group A (on Metformin) & Group B (Non-Metformin)

Groups	% of Predominant Macrocytic	% of Mixed (Macrocytic+microcytic)	% of Predominant normocytic & Normochromic	χ^2	P Value
A	50 %	38.88%	11.11%	0.115	0.98*
B	42.85%	42.85%	14.25%		

* Statistically no significant.

This table showing GBP feature of vitamin b12 deficient patient of Group A (on Metformin) & Group B (Non-Metformin) statiscally not significant (p value 0.98).

Table 8: Correlation Of Variables With Vitamin B12 In Group B (Non- Metformin)

	Variable	N	Pearson's correlation Coefficient
VITAMIN B12	Age	90	r = -0.187
	Duration of DM	90	r = -0.449**
	FBS	90	r = 0.01
	PPBS	90	r = 0.184
	HB1Ac	90	r = -0.181
	Insulin dose	66	r = -0.266
	Insulin duration	66	r = -0.097
	Other drugs	24	r = 0.303

In Pearson Correlation analysis, significant negative correlation was seen between duration of Diabetes and B12 levels among the 90 patients taking Insulin therapy. The other variables were not significantly correlated.

Table 9: Correlation Of Variables With Vitamin B12 in Group A (Metformin)

	Variable	N	Pearson's correlation Coefficient
	Age	90	r = -0.287
	Duration of DM	90	r = -0.339*
	FBS	90	r = 0.02
	PPBS	90	r = -0.167
	HB1Ac	90	r = -0.21
	Metformin dose	90	r = -0.572**
VITAMIN B12	Metformin duration	90	r = r = -0.407*

Among cases (patients taking Metformin), statistically high significant correlation (r >.3) was obtained between Metformin use dose and duration and B12 levels decreases as metformin use increases (Negative correlation) Duration of diabetes and B12 levels were also negative and significantly correlated.

Table 10: Relationship Of Metformin Dose And Duration With Vitamin B12 Level Group A (on metformin)

Vitamin 12 category					
	Deficient	Borderline deficient	Normal	Total	P Value
Daily metformin dose in mg					
<2000	4	9	17	30	
>2000	14	21	25	60	
Mean daily metformin dose in mg ±SD	1981 ± 222	1849 ± 422	1695±494	1758±467	<.001
Duration of metformin use in years					
<4	6	10	13	29	
>4	12	20	29	61	<.001

In above table our study showing the Group A (on Metformin) found significant association with duration of metformin & dose of metformin taken by patient.

DISCUSSION

Vitamin B12, an essential micronutrient which is required for optimal hemopoetic, neuro-cognitive and cardiovascular function. High prevalence of Biochemical and clinical vitamin B12 deficiency have been demonstrated with diabetes mellitus. It presents with wide range of clinical manifestations from megaloblastic anaemia pancytopenia impaired memory, dementia, delirium, peripheral neuropathy, sub-acute combined degeneration of the spinal cord. Increased frequency of vitamin B12 deficiency among the diabetic patients has been documented in several cross sectional studies and case reports. The prime factor associated with vitamin B12 deficiency among patients with DM is Metformin use. The prevalence of vitamin B12 deficiency due to metformin use range from 5.8% to 33%. The varied study definitions of vitamin B12 deficiency explains the wide variation of the reported prevalence.

In the National Health and Nutrition Examination Survey of 1999– 2006 in the USA "defined definite and borderline biochemical vitamin B12 deficiency as serum vitamin B12 concentrations of ≤148 pmol/l and >148- 221 pmol/l respectively" .In one cross sectional study that documented a high prevalence of vitamin B12 deficiency of 33% among adult patients with

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T2DM vitamin B12 deficiency was defined as" serum vitamin B12 concentrations <150 pg/ml ".patients who were on high dose (>2 g/day) and long term (4 years)metformin treatment were enrolled in this study, both clinical factors known to be associated with vitamin B12 deficiency.

In this cross sectional study, 180 DM patients were enrolled and they were divided in two groups thosewho are taking metformin (group A) where as patients on insulin and other oral hypoglycemic agents are in group B.

The cases on metformin had the prevalence of vitaminB12 deficiency is 20% which is significance onregards to another group. It is also dependent on the dose and the duration of drug and the duration of disease. But in the group B the Vitamin B12 deficiency prevalence is 7.6%

In this among the group B had 7 person low vitamin level and 18 had border line level, 65 had normal/high level which comes in the following % respectively7.7,20 &72.3 where as in Group A it is had 18person low vitamin level and 30 had border line level, 42 had normal/high level ,which comes in the following

% respectively 20 ,33.33 &46.66so metformin group had noticeable vitamin B12 deficiency prevalence comparing to group B. When study of both group A (on metformin) ,B (non-metformin) were analyzed by using chi square test highly statistical significant p value obtained.

When study participants were analyzed for intergroup differences in B12 levels, the mean difference in B12 levels between GroupB (Insulin+ non biguanide OHA) and GroupA (Metformin) group was 356.70mcg/dl, and when independent t- test was applied, highly statistical significant values with p values <.001 was obtained.

In our study patients did not take any drug such as chronic therapy of PPI,H2 Blocker , and chloramphenicol, etc.

Irish defined levels of less than 100 pg/ml as vitamin B12 deficiency but as per the Indian guide lines we included 240-900μmol/l5 among cases (patients taking Metformin), statistically high significant correlation (p value <.001) was obtained between: Metformin use and B12 levels (i.e., B12 level decreases as metformin use increases –Negative correlation).

Ting et al, noticed dose of metformin duration are main factors for Vitamin B12 deficiency .This is similar to our study showing noteworthy association and opposite relation dose, duration of metformin with B12 levels.

CONCLUSION

This cross-sectional comparative study concludes that the persons with DM on chronic metformin therapy showed lower levels of serum vitamin B12 status compared to persons not treated with metformin. This represented that metformin takes a possible risk for vitamin B12 deficiency. The study highlights the need of testing B12 level, when patients are prescribed metformin for long period there by preventing from its impending side effects.

The study recommends base line B12 levels in high risk patients before starting metformin therapy. Italso recommend vitamins screening if therapy is advised high dosage of metformin for prolonged periods to avoid the neuropathic complication which are more common in diabetics due to the advanced glycation end products. Doctors treating DM should consider this significant point when treating diabetic patients with metformin, and particularly with those who present with neuropathic signs and symptoms.

The study also recommends patients may have vitamin B-12 deficiency despite of absence of anemia and change in general blood picture ;

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