

Importance of Vitamin B12 for Diabetic Patients Treated with Metformin

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ABSTRACT

Metformin is among the most frequently prescribed medication for type-2 diabetes Miletus. It has been diversely approved through research studies that it suppresses the hepatic glucose production along with boosting insulin signalling in muscles, adipose and hepatic tissues. As an observation on a long-term basis, it has shown the deficient results causing anaemic condition. Some studies have reflected that longer duration of metformin use decreases the level of vitamin b12 that is considerably more than 2000 mg/d with four years of study. Its prevalence has increased worth more duration and doze in use, with an exceptional peripheral neuropathy that is the only clinical presentation without any symptoms of hematological signs. Presently, there are no obvious guidelines except the consideration of level in perspective of level of metformin on different doze. We have explored different studies, by consulting the literature work and exploring its relevance with the doze intake.

Key words: Metformin, Diabetes miletus, Insulin, Vitamin-B12

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INTRODUCTION

According to world health organization and international diabetes federation, 422 million people were analyzed with diabetes mellitus in 2014 with a surge as compared to 108 affected people in 1980. Its prevalence is increasing, mainly in the developing countries as in Pakistan with an estimation of 10.6% of urban population and rural in 7.7% suffering with this disease.

This disease is because of either insulin resistance or relative lack of insulin, for which different options are considered. It has various side effects of metformin like lactic acidosis, diarrhoea, and abdominal discomfort. Additionally, its utilization has been linked with serum vitamin b12 deficiency in various studies.

But the consideration of level of serum vitamin b12 is important, resultantly the vitamin B12 deficiency attained in patients on metformin, replacing of vitamin B12 or its withdrawal will enhance patient's condition. Our study investigates the variation with different levels; most of the cases would be in diabetic patients due to its relevance with it.

Moreover, if the notable vitamin b12 deficiency is evaluated in association with metformin, then general guidelines might be formulated based on literature survey, to give a direction for an early b12 replacement in order to avoid complications. Our main goal of study is to govern their role and link with of vitamin b12 and metformin [1].

Diabetes mellitus is known to be most common endocrine disorder that sixth among those that often leads to death for which metformin is prescribed mutually. It is considered as a cornerstone in type-2 diabetes and

regarded as an oral hypoglycaemic agent due to its increased tolerance among most patients.

It's associated as antihyperglycemic agent that boosts the cardiovascular mortality and morbidity; that results in deaths of diabetic patients. In 1969, it was observed that metformin and proton pump inhibitors are renowned for causing vitamin b12 deficiency because of an inducing action on calcium dependent membrane that leads to malabsorption of vitamin b12 in terminal ileum.

On an average 6-30% of patients could probably show the finding of this deficiency, but is also regarded in some observations as conversing the effect to duration and doze of metformin use. Additionally, this treatment is reportedly linked with decreasing folate concentration, although its mechanism is yet explored.

Conclusively, decrease in both vitamin b-12 and folate concentrations result in enhancing homocysteine concentration that is known to be an independent risk factor for cardiovascular disease, mainly among the individuals with type-2 diabetes. For this purpose, American association of treatment has guided regular monitoring guidelines of vitamin b12 levels among the patients with diabetes and taking metformin.

Meanwhile, the observations on serum vitamin b12 have explored varied results by showing an unreliable marker of decreasing vitamin b12 due to varied observation and measurement methods. The keystone in one-carbon pathway is homocysteine in a methionine metabolism that has an influencing role in DNA methylation and plays an important role in intracellular vitamin b12 reactions.

Its increased level is connected with more cognitive disorders, cardiovascular disease, chronic diseases, and cancer that are the result of vitamin b12 deficiency. Thus, for accurate results of vitamin b12 deficiency in tissues there is a need of monitoring increased homocysteine with serum vitamin b12 among patients.

Diverse literature survey reflects increased homocysteine as increasing the vitamin b12 deficiency through metformin, but controversial studies are also available. This controversy is mainly referred as the clinical significance of metformin induced vitamin b12 deficiency; in which peripheral nerve damage and anemia are typical symptoms.

Among which if the peripheral nerve damage is not properly treated, then diabetic peripheral neuropathy could be exasperated causing the serious nerve damage. In this concern, the vitamin b12 deficiency is not attributed with metformin treatment.

Conversely, the consumption of meat in Asian countries is relatively lower than Westerns, referring higher risk of vitamin b12 deficiency, but only few studies have explored the doze and duration of metformin in this contextual way.

Considering different studies, the prospect of placebo-controlled studies is being conducted to state the risk of metformin-induced individuals with vitamin b12 deficiency and not mainly in prediabetic individuals. In

this context different randomized trials for short durations among the patients with type 2 diabetes in relevance to polycystic ovary syndrome.

Researches in this domain has shown varied results, and the longest prospect on those randomized trail reflected vitamin B12 with almost 4.3 years, showing deficiency of vitamin b12 with metformin by 19%, more homocysteine concentration by 5% and was linked with 11-fold more risk in low vitamin b12 level as compared to placebo.

Vitamin b12 is a water-soluble vitamin that has a fundamental role in neurological functioning, optimal homeostasis, DNA synthesis, and is vital nutrient for health. Although, the clinical predictions being observed are predominately of neurological dysfunctioning and hematological consent.

It's typical observation shows that the decrease in vitamin b12 absorption along with levels following the metformin starts at the 4th month [2-5]. It's generally proposed mechanism among the T2DM patients include variations in small bowel motility that enhances the bacterial outgrowth, leading to vitamin b12 deficiency, its inactivation and alteration in the intrinsic factors.

It might show serious outcomes like megaloblastic anemia, neuropathy, linked with dementia that is linked with metformin a vitamin b12 deficiency. Its recent cohort study has shown a potential risk of vitamin b12 deficiency, among patients with long-term analysis, in similar metformin treatment for diabetes that exhibits lower holotranscobalamin and serum cobalamin, and more Hcy as compared to patients that are not exposed to metformin treatment.

This has highlighted different contexts that clearly depict the necessity of evaluating b12 status during the treatment of metformin, to avoid adverse consequences and preserving the advantageous affects as well [4].

Our approach in this study is to consider different experimental evaluations to validate our concerns on vitamin b12 and metformin, that would be effective in future study.

Our objectives correlating with diverse literature would show different outcomes with respect to varying concentrations. It would then direct future perspectives of continuous evaluation of this prescribed treatment in order to show positive consequences in future with the low and higher level of treatment [6,7].

METHODOLOGY

A detailed literature survey was conducted with the inclusion of different patients that were enrolled and prescribed with the treatment that is our subject of concern. The literature concerned was from Google Scholar, PubMed, Science direct, and Elsevier. This was consulted with respect to diverse work being done on vitamin b12 and metformin under different perspectives.

RESULTS AND DISCUSSION

The relationship among the vitamin b12 serum and metformin has shown potential factors involved in the

clinically studied population that has shown different results (Table 1).

Table 1: Two targeted groups and vitamin b12 [8].

Factors	Vitamin b12 deficiency	Normal Vitamin B-12
Age	60.1 ± 11.6	59.3 ± 10.7
Male	148 (59%)	497 (57%)
Diabetes duration, yr.	11.4 ± 7.0	10.2 ± 6.9
Hypertension, %	179 (72.9%)	574 (66)
	Metformin duration, yr.	
<10	110 (44.5)	480 (55.6)
10-<20	104 (42.2)	320 (35.0)
	Metformin doze mg/d	
<1000	21 (8.5)	202 (23.4)
1000-<1500	37 (15.0)	215 (24.9)

This serum vitamin b12 has shown negative correlation with metformin doze but is not observed to be correlated with its duration as was observed in our study. This has shown varied studied results with characterized factors. This has explored that with respect to age the observations were observed in normal and deficient vitamin b12 that has shown division into two groups with annual metformin duration and doze with the factors including BMI, and fasting glucose, neuropathy, anemia, haemoglobin, diastolic and systolic BP, cholesterol level, multivitamin agents, folate, and insulin use that were considered among people of two groups in which sex, age, cardiovascular, BMI has not shown any difference. Its graphical presentation of four groups has shown decrease in serum vitamin b12 deficiency with an increase in metformin (Figure 1 and Table 2) [7].

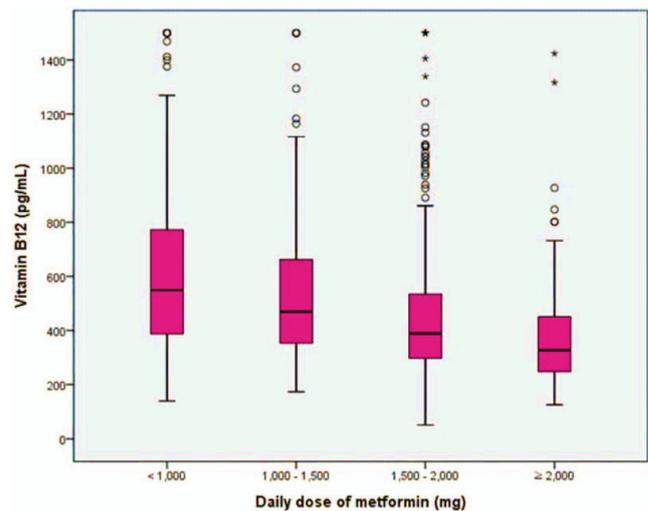


Figure 1: Metformin doze and vitamin b12 in four groups.

Table 2: The variation in duration and doze of metformin [6].

Serum vitamin b12	Metformin duration		Metformin doze	
	Beta	p-value	Beta	p-value
Crude	0.03	0.317	-0.299	<0.001
Model 1	-0.913	0.853	-0.159	<0.001
Model 2	5.289	0.183	-0.142	<0.001

Our observations have shown different results with prevalence of vitamin b12 deficiency among the diabetic patients taking metformin as a long-term duration and a regular doze linked with vitamin b12 deficiency. In this concern, our study has shown factors that are associated with it are ALT levels, age, multivitamin supplements, anemia, and alcoholic consumption. These were linked directly or indirectly having their consequences over the outcomes as the level variation comes under this

concern. But the metformin use has not shown any significant results and serum homocysteine has negative correlation with serum vitamin b12 level as was observed in our study along with altered results in both targeted groups [3]. Other studies on vitamin B12 and metformin have shown different results that are explained below, with varied discussion points and prevalence to the disease (Table 3).

Table 3: Different prospects of disease, doze, and vitamin b12 with metformin.

Disease	Metformin duration/ doze	Vitamin b12 status	Reference
Diabetes type 2	12 months	Those having vitamin b12 less than 150 pg/ml were deficient in b12	[2]
Out-patient study	Long term treatment	Risk of vitamin b12 increases to deficiency along with homocysteine	[6]
Type 2 diabetes	16 weeks	Low folate and vitamin b12	[4]
DM (60 patients in which 32 were taking metformin of 58 age and 28 of 59 age were not)	<150 pmol/l	Serum mean was 424 ± 158 pg/ml among metformin patients and 619 ± 177 pg/ml in not taking metformin	[5]
Its relevance with diabetic neuropathy	Chronic metformin use in 162 patients	Low level in 7.3% patients, diabetic neuropathy with b12 level of 64% as compared to non-diabetic with 17%	[7]
209 diabetic patients	4 months with over 45 years age taking for 3 months	Almost 29% of patients have shown deficiency, its prevalence was more in the smoking people and those taking multivitamins has shown low deficiency	[9]
DM in tertiary care hospital	7 months with age 18 or more	A significant concentration has not shown any drop in vitamin b12	[10]
Supplements of vitamin b12 in DM	Adults over 50 years	Biochemical b12 deficiency was more in diabetic patients with metformin as compared to non-diabetic	[7]

This has shown that the significantly more prevalence of vitamin b12 deficiency among patients treated with metformin with an impact of duration and doze, for which physicians should understand this fact and screen diabetics on its therapy for b12 deficiency [10]. It is also well known now that this deficiency is increased with age, as an observation has shown that elderly was affected 20%, that varies among people depending on the population being studied and B12 cut-off use. The survey conducted by national health and nutrition examination in 1990's to 2000's has reflected that metformin prescribed remediation is linked with b12 deficiency [7]. Few studies have shown no significant effect on peripheral neuropathy on taking metformin. A study being conducted in France has recognized that cobalamin deficiency linked with metformin has shown 6% of incidence of vitamin b12 deficiency that resulted in peripheral and hematological anomalies [8]. Moreover, its association with biochemical b12 deficiency is highly prevalent, the institute of medicine has represented that amount of B12 should be 2.4 microgram per day, and the ratio in the multivitamin is generally not enough to remediate this deficiency along with diabetes [6]. Its evaluation in the tertiary care hospital has shown different results, as the vitamin b12 was not deficient among the diabetic patients on metformin, instead all patients were observed to be facing neuropathy, which explores that it is not related to metformin induced vit-B12 deficiency [9]. Another study conducted has shown its prevalence varying more in smoking patients as compared to non-smokers, because those diabetic patients were having higher chances of vitamin b12 deficiency. Therefore, this element should also be recognized in future by the clinicians which are recommending metformin should be screening this, and the multivitamins being taken have its own protective

role among patients. This has shown different studies, based on the experimental analysis and have suggested ways to cope the diabetes by regular monitoring of metformin doze and use with respect to patient's age, weight, and disease level. There is a need of regular screening by the health professionals in patients taking this treatment for few or relatively long period of time [11-16].

CONCLUSION

Diabetes is a common health problem globally, which often leads to various complications like neuropathy, for which metformin is a mainly prescribed treatment. Its relevance with serum vitamin b12 has an association with deficiency that is more common among the diabetic patients as compared to the non-diabetics observed under our study. Long-term therapy of metformin often leads to vitamin b12 deficiency, that should be monitored because it is also observed to be causing homocysteine increase that causing chronic diseases. There is yet more research to be done on optimal vitamin b12 supplementation with frequency and doze among affected people.

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