

# Metformin related Vitamin B12 Deficiency: an important Comorbid Factor in Diabetic patients

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## ABSTRACT

**Background:** Metformin decreases vitamin B12 absorption by tying up free calcium required for absorption of the intrinsic factor-B12 complex.

**Aims:** A cross sectional study was designed to find out the relationship of vitamin B12 deficiency with impaired blood glucose and dyslipidemia in diabetic patients taking metformin.

**Methods:** Six month based (Jan 2010 to June 2010) cross-sectional study was carried out. 50 male diabetic patients visiting outdoor department of Sir Ganga Ram Hospital with age range 40-60 were included in the study. Their duration of diabetes was 3-8 years. Patients taking insulin, lipid lowering drug, history of ketosis, any infection, having nephropathy were excluded from the study. Their BMI and blood pressure was noted.

Blood sugars and lipid profile were estimated by standard kits of Merck using Auto analyzer. Injection of vitamin B12 (500 µgm) obtained from Hilton Pharma Private Limited Lahore was injected I/M after every 15 days. Baseline investigations were repeated at the end of one month.

**Results:** Level of fasting blood sugar and postprandial sugar was significantly decreased ( $P<0.001$ ) after therapy of I/M injection of vitamin B12. Level of serum cholesterol, triglyceride and LDL-chol was also decreased after therapy of vitamin B12, but significant difference ( $P<0.001$ ) was only observed in case of serum cholesterol. Level of HDL-chol was significantly increased ( $P<0.001$ ) after vitamin B12 therapy.

**Conclusion:** It is therefore concluded that that physician should consider vitamin B<sub>12</sub> deficiency during management of comorbidities of diabetes, especially dyslipidemia.

**Keywords:** Vitamin B12, Metformin, Diabetes

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## INTRODUCTION

Comorbidity has bad effects on the quality of life in diabetics<sup>1</sup> especially negative effects on their emotions and disease management<sup>2</sup>. Comorbidity was found in 40% diabetic patients. However Prevalence rate of comorbid results of vitamin B12 deficiency is in a range of 12-23% in diabetic patients with age greater than 60 years and they are affected with complication of neuropathy<sup>3,4</sup>.

Diabetes is a disease of inflammation and oxidative stress<sup>5</sup>. Vitamin B12 considered as an antioxidant and it plays an important role in neurocognitive, hemopoetic and cardiovascular function. Its decreased level may increase oxidative stress, in diabetic patients<sup>6,7</sup>. Its deficiency may also have a role in peripheral neuropathy, delirium, impaired memory, megaloblastic anemia and spinal cord degeneration<sup>8</sup>.

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Metformin is taken as a keystone in the management of diabetes. The useful effects of drug is decreased the level of blood sugar and of lipid profiles. However its treatment is also responsible for comorbidity<sup>9</sup>. According to the survey from NHANES 1999–2006, prevalence of deficiency of vitamin B-12 is 5.8% in diabetes taking metformin as an oral hypoglycemic drug<sup>10</sup>. Lately it is reported that the incidence of vitamin B12 deficiency was 14.1% in diabetics using metformin and decreased upto 4.4% in patients using other hypoglycemic drugs<sup>11</sup>. It is proposed that Metformin decreases vitamin B12 absorption by tying up free calcium required for absorption of the IF-B12 complex<sup>12</sup>.

It is known that high level of LDL-chol and serum cholesterol may increase the risk of atherosclerosis in diabetics. Experimentally it is proved that LDL in its oxidized form may be a cause of oxidative stress and responsible for hypercholesterolemia<sup>13</sup>. However antioxidants have the ability to lower the LDL susceptibility to oxidation by disrupting the chain reaction associated with peroxidation of free radical and prevent endothelial dysfunction<sup>14</sup>.

There was a direct link between the serum level of fructosamine and total vitamin B12 binding capacity in poorly controlled diabetic patients and the

low level of fructosamine was associated with the alteration of total vitamin B12 binding capacity and serum levels of vitamin B12 levels in diabetic patients. These results show role of vitamin B12 in glycemic control in diabetes mellitus<sup>15</sup>.

Metformin is most frequently used hypoglycemic drug in diabetics as it has mild side effects however the effect of metformin on developing vitamin B12 deficiency is overlooked and hardly investigated. It is therefore a need to find out therapeutic effect of vitamin B12 on blood glucose and lipid profile (comorbid factors) in diabetic patients taking metformin.

## PATIENTS AND METHODS

Six month based (Jan 2010 to June 2010) cross-sectional study was carried out. 50 male diabetic patients visiting outdoor department of Sir Ganga Ram Hospital with age range 40-60 were included in the study. Their duration of diabetes was 3-8 years. Patients taking insulin, lipid lowering drug, history of ketosis, any infection, having nephropathy were excluded from the study. Their BMI and blood pressure was noted. Letter of consent was taken from each patient.

Daily dietary intake of vitamin B12 of every patients was calculated by table of selected food sources of vitamin B12 by U.S. Department of Agricultural Research 2003 (USDA Nutrient Database) and compared with RDA (Institute of Medicine USA).

Blood sample was drawn from patients for estimation of fasting and postprandial blood glucose, total serum cholesterol, triglyceride, HDL-cholesterol and

LDL-cholesterol before and after treatment with vitamin B12. Blood sugars and lipid profile were estimated by standard kits of Merck using Auto analyzer. Injection of vitamin B12 (500 µgm) obtained from Hilton Pharma Private Limited Lahore was injected I/M after every 15 days. Baseline investigations were repeated at the end of one month.

**Statistical analysis:** Data was entered and analyzed by SPSS 16.0. Mean and standard deviation were calculated. Variables were compared by student 't' test. P value <0.05 was taken as significant.

## RESULTS

Variation in the level of blood sugar and lipid profile in male diabetic patients before and after methcobalamine (vit B12) therapy is tabulated (Table). It is observed that the level of fasting blood sugar and postprandial sugar was significantly decreased (P<0.001) after therapy of i/m injection of vitamin B12. Level of serum cholesterol, triglyceride and LDL-cholesterol was also decreased after therapy of vitamin B12, but significant difference (P<0.001) was only observed in case of serum cholesterol. Level of HDL-cholesterol was significantly increased (P<0.001) after vitamin B12 therapy.

Diabetic patients with fasting glucose ≥140 mg/dl and HbA1c ≥6.5% and using metformin drug were included in the study. Patients with renal or liver disease and using vitamin B-12 or any antioxidant as supplement were excluded from the study. Letter of consent was taken from each patient and an approval was taken from the Institutional Review Board of Sir Ganga Ram Hospital Lahore.

Table: Variation in the level of blood sugar and lipid profile in male diabetic patients before and after methcobalamine (vit B12) therapy

Methcobalamine therapy	Fasting blood sugar(mg/dl)	Postprandial blood sugar(mg/dl)	Total cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)
Before injection	157.18 ±7.46	236.14 ±6.87	201.45 ±5.80	165.39 ±17.03	36.12 ±0.76	132.26 ±5.22
After injection	130.14 ±5.50**	200.25 ±6.45**	190.27 ±3.85	171.14 ±13.62	39.38* ±0.59	116.50 ±3.38

## DISCUSSION

Metformin a hypoglycemic drug may be responsible for the deficiency of Vitamin B-12<sup>16</sup>. Normally vitamin B12 may act as antioxidant, modifying signaling molecules to lower the oxidative stress<sup>17</sup>. Additionally it also an anti-inflammatory agent via stimulation of oxidative phosphorylation and inhibition of the activity of nitric oxide synthase<sup>18</sup>.

Present study observed a significantly decreased level of fasting blood sugar and postprandial sugar after of i/m injection of vitamin

B12. According to a study diabetic patients with lower vitamin B-12 status had significantly higher levels of blood glucose as it may impair glucose tolerance<sup>19</sup>. It is stated that Vitamin B-12 plays a main role in the consumption of glucose, and its deficiency may cause high blood sugar level. Experimentally it is proved that decreased level of vitamin B12 may lower the level of glutathione and the activity of enzymes of carbohydrate metabolic pathway and study found an important role of vitamin B-12 for the regulation of glucose<sup>20</sup>. Another study found that vitamin B12 deficiency altered the glucose uptake which is mainly

stimulated by insulin. This may increased the activities of gluconeogenic enzyme in liver. It is therefore concluded that lower level of vit B12 may lowered the antioxidant status had elevated the oxidative stress<sup>21</sup>.

We observed that the level of serum cholesterol, triglyceride and LDL-chol was also decreased after therapy of vitamin B 12, but significant difference ( $P < 0.001$ ) was only observed in case of serum cholesterol. A study also observed a negative correlation between lipid profile and vitamin B-12<sup>22</sup>. This showed that the status of Vitamin B-12 status is positively link inflammation and oxidative stress<sup>19</sup>. Another study stated that increased level of serum cholesterol is related with atherosclerosis and it also play a role in increasing the oxidative stress<sup>23</sup>.

## CONCLUSION

It is therefore concluded that that physician should consider vitamin B<sub>12</sub> deficiency during management of comorbidities of diabetes, especially dyslipidemia.

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