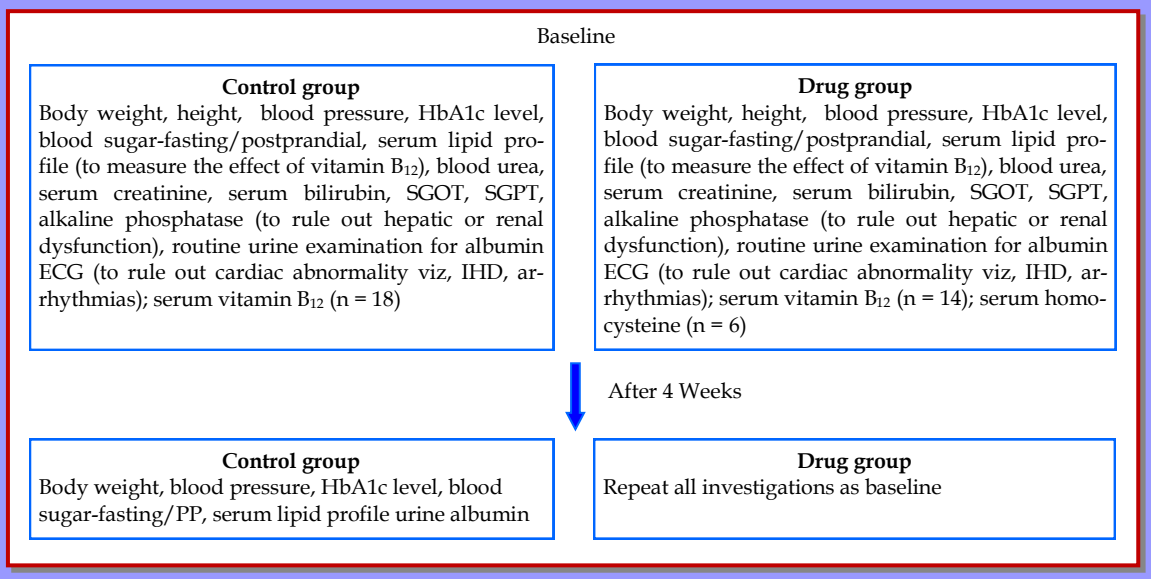


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# Effect of vitamin $B_{12}$ supplementation on glycemic control in poorly controlled hyperhomocysteinemic type 2 diabetic patients

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## Abstract

This study was conducted to observe the effect of vitamin $B_{12}$ supplementation on glycemic control in poorly controlled hyperhomocysteinemic type 2 diabetic patients by measuring HbA1c levels at baseline and 4 weeks. Patient having serum homocysteine more than 15 µmol/L or vitamin $B_{12}$ less than 223 pg/mL were enrolled in this study. One group received methylcobalamin 500 µg daily with their usual anti-diabetic therapy and the other group received only suitable anti-diabetic drug therapy. Methylcobalamin 500 µg was given daily for period of 4 weeks. Glycemic control was measured by levels of HbA1c, blood sugar at baseline and at 4 weeks. Serum homocysteine levels was reduced from 21.5 ± 2.6 to 15.4 ± 6.4 ($p=0.04$) with vitamin $B_{12}$ supplementation at 4 weeks. At 4 weeks, HbA1c decreased from 9.9 ± 0.9 to 8.7 ± 0.5 ($p<0.01$) in vitamin $B_{12}$ deficient patients after vitamin $B_{12}$ supplementation. There is role of vitamin $B_{12}$ in glycemic control in poorly controlled type 2 diabetic patients.

## Introduction

Hyperhomocysteinemia is observed in type 2 diabetes and it is associated with macroangiopathy, nephropathy and microalbuminuria (Buysschaert et al., 2000; Jager et al., 2001). Hyperhomocysteinemia is a risk factor for atherosclerosis (Mahendran et al., 2013). Moderately raised plasma homocysteine was obtained with associated decreased folic acid and vitamin $B_{12}$ levels in type 2 diabetes subjects (Soinio 2004; Klee 2000; Ebesunun and Obajobi, 2012). Raised homocysteine levels are associated with raised levels of bad cholesterol and decreased levels of good cholesterol (Mahendran et al., 2013; Ramachandran et al., 2012).

Homocysteine is independently associated with the prevalence of diabetic neuropathy in type 2 diabetic patients (Ambrosch 2001). Metformin also causes vitamin $B_{12}$ deficiency. There is no evidence that pathological levels of the biochemical markers of $B_{12}$ are more common in metformin-treated compared with non–metformin-treated patients, despite lowering $B_{12}$ in serum or plasma (Obeid, 2014).

Vitamin $B_{12}$ 100 µg alternate day with low fat vegan diet resulted in improvement in glycemic and lipid control (Barnard et al., 2006) Therapy with folic acid, vitamin $B_{12}$, and vitamin $B_6$ significantly decreases the incidence of major adverse events after percutaneous coronary intervention (Schnyder 2002). This study was planned to study effect of vitamin $B_{12}$ supplementation on glycemic control in poorly controlled hyperhomocysteinemic type 2 diabetic patients with objectives: a) glycemic control measured by levels of glycosylated hemoglobin (HbA1c) at baseline and 4 weeks; b) fasting blood sugar level at baseline and 4 weeks; c) serum homocysteine/vitamin $B_{12}$ levels at baseline and 4 weeks; d) serum lipid profile at baseline and 4 weeks.

## Materials and Methods

Patients not responding adequately to oral anti-diabetic agents were recruited from Medicine OPD with the help of treating physician. Patient were first screened for serum homocysteine/vitamin $B_{12}$ level along with all baseline investigations. Those having serum homocysteine level more than 15 µmol/L or vitamin $B_{12}$ level less than 223 pg/mL were enrolled in this study. Due to high cost for investigation, serum homocysteine level was measured only in 6 patients and serum vitamin $B_{12}$ level was measured in 14 patients with prior permission from Ethics Committee.

Inclusion criteria for this study were: Age between 30 - 70 years, male, non-lactating female, HbA1 >8%, serum homocysteine >15 µmol/L or serum vitamin $B_{12}$ level <223 pg/mL ischemic heart disease (IHD) or non-IHD patients. Exclusion criteria were: Age <30 years, pregnancy, lactating mother, patient with insulin dependent diabetes mellitus, severe and complicated diabetes, patients with hepatic or renal dysfunction. After enrolment of patients for the study, all the baseline investigations were carried out at Central Clinical Laboratory except Hb1Ac which was carried out at Department of Pharmacology. Serum homocysteine or vitamin $B_{12}$ estimation was carried out in an accredited laboratory. There were two groups of poorly controlled patient; Drug group received methylcobalamin 500 µg daily with their usual anti-diabetic therapy and the control group received suitable anti-diabetic drug therapy as prescribed by treating physician. Methylcobalamin 500 µg was given once daily for the period of 4 weeks and were followed-up at 4 weeks. At baseline all the investigations were carried out (Figure 1).

### *Reporting of adverse effects*

All patients were given checklist of adverse effects of vitamin $B_{12}$ and information about adverse drug reactions was collected in follow-up. Patients unable tolerate adverse drug reactions, were advised to contact any of investigators at any time for review and advice.

### *Sample size calculation and statistical analysis*

Sample size of 20 for each group was calculated in the ratio of 1, power 80%, considering 10-fold difference of drug effect in vitamin B12 group and control group by using Open Epi 2.3 (2009). Randomization was done with the help of randomization software (Rando 1.2, 2004). Statistical analysis was done by using Open Epi 2.3, 2009) and Microsoft Excel.

## Results

In this study, 20 patients completed study in drug group and 18 patients in control group. There was no significant difference in demography in both the groups. There was no significant difference in baseline parameters (Table I)

There was significant fall in serum homocysteine levels with vitamin $B_{12}$ supplementation in hyperhomocystenemic type 2 diabetic patients at 4 weeks. No significant fall in blood sugar levels and HbA1c levels was observed after vitamin $B_{12}$ supplementation in hyperhomocystenemic type 2 diabetic patients at 4 weeks. No significant beneficial effect was observed on lipid profile at 4 weeks after vitamin $B_{12}$ supplementation (Table II).

There was significant rise in vitamin $B_{12}$ levels and significant fall in HbA1c levels in vitamin $B_{12}$ deficient patients with vitamin $B_{12}$ supplementation at 4 weeks (Table III).

Combined data of poorly controlled hyperhomo-

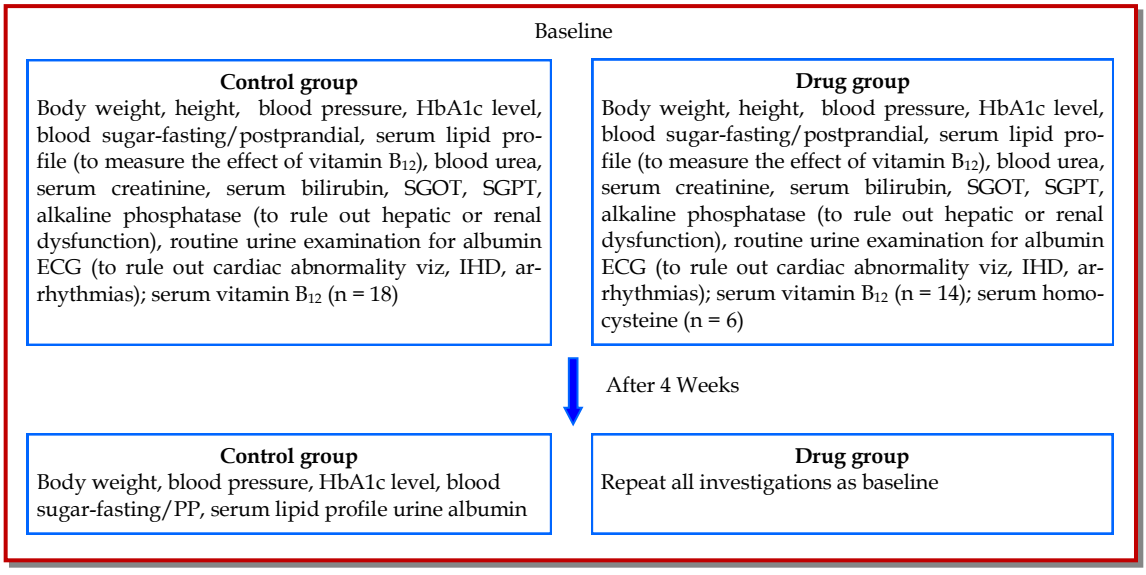


Figure 1: Flow chart of investigations

**Table I**

**Demographic characteristics**

| Parameter | Drug group (n=20) | Control group (n=18) |
|---|---|---|
| Sex | | |
| Male | 3 (15%) | 4 (22.2%) |
| Female | 17 (85%) | 14 (77.7%) |
| Age (years) | 51.8 ± 8.9 | 55.1 ± 7.9 |
| Weight (kg) | 61.0 ± 5.9 | 60.8 ± 11.9 |
| HbA1c (%) | 10.0 ± 0.8 | 9.3 ± 1.0 |
| Fasting blood sugar level (mg/dL) | 157.6 ± 61.3 | 132.1 ± 29.7 |
| Postprandial blood sugar level (mg/dL) | 239.2 ± 111.2 | 208.7 ± 62.3 |

Data are mean ± SD

cystenemic and vitamin B12 deficient type 2 diabetic patients had shown significant fall in HbA1c levels at 4 weeks (Table IV).

## Discussion

In this study, a dose 500 µg/day was used orally for 4 weeks in poorly controlled type 2 diabetic patients with either hyperhomocysteinemia or vitamin $B_{12}$ deficiency. There was significant decrease in levels of homocysteine from 21.5 ± 2.6 to 15.4 ± 6.4, (p=0.04) with vitamin $B_{12}$ supplementation for four weeks. In vitamin $B_{12}$ deficient and hyperhomocystenemic type 2 diabetic patients, there was significant decrease in HbA1c levels from 9.9 ± 0.9 to 8.7 ± 0.5, (p<0.01) with vitamin $B_{12}$ supplementation for 4 weeks. This study has proved that vitamin $B_{12}$ alone can also reduce homocysteine level in hyperhomocystenemic type 2 diabetic patients.

In adult patients with type 2 diabetes, intra muscular or oral vitamin $B_{12}$ in doses of 1000 µg daily for a week then once every week for 4 weeks are sufficient to correct vitamin $B_{12}$ deficiency (Kibirige and Mwebaze, 2013). Vitamin $B_{12}$ 100 µg alternate day with low fat vegan diet resulted in improvement in glycemic and lipid control (Barnard et al., 2006). Therapy with folic acid, vitamin $B_{12}$, and vitamin $B_6$ significantly decreases the incidence of major adverse events after percutaneous coronary intervention (Schnyder et al., 2002). Vitamin $B_{12}$ replacement has been shown to cause symptomatic improvement among patients with severe diabetic neuropathy (Kibirige and Mwebaze, 2013; Talaei et al., 2009).

As higher homocysteine level in poorly controlled type 2 diabetic patient is associated with poor glycemic control (raised HbA1c) and micro-macro vascular complication (Ramachandran et al., 2012), correction of homocysteine level and correction of vitamin $B_{12}$ deficiency which is one of the factor raised homocysteine level would have resulted in beneficial improve-

**Table II**

**Vitamin $B_{12}$ supplementation on glycemic control and lipid profile in hyperhomocystenemic poorly controlled type 2 diabetic patients**

| Parameter | Baseline | After 4 weeks | p value |
|---|---|---|---|
| Serum homocysteine (µmol/L) | 21.5 ± 2.6 | 15.4 ± 6.4 | 0.04 |
| HbA1c (%) | 10.0 ± 0.6 | 9.8 ± 0.8 | 0.57 |
| Fasting blood sugar level (mg/dL) | 181.5 ± 99.8 | 152.5 ± 65.1 | 0.57 |
| Postprandial blood sugar level (mg/dL) | 300.3 ± 193.8 | 260.6 ± 146.7 | 0.69 |
| HDL (mg/dL) | 41.9 ± 12.5 | 44.2 ± 12.1 | 0.75 |
| Total cholesterol (mg/dL) | 159.3 ± 25.4 | 156.8 ± 36.5 | 0.89 |
| Triglycerides (mg/dL) | 108.1 ± 32.5 | 105.9 ± 41.6 | 0.92 |

Data are mean ± SD

**Table III**

**Vitamin $B_{12}$ supplementation on glycemic control in vitamin $B_{12}$ deficient poorly controlled type 2 diabetis**

| Parameter | Baseline | After 4 weeks | p value |
|---|---|---|---|
| Serum vitamin $B_{12}$ (pg/mL) | 203.8 ± 17.6 | 515.1 ± 77.4 | <0.01 |
| HbA1c (%) | 9.9 ± 0.9 | 8.7 ± 0.5 | <0.01 |
| Fasting blood sugar level (mg/dL) | 147.3 ± 35.9 | 130.3 ± 32.6 | 0.21 |
| Postprandial blood sugar level (mg/dL) | 213.0 ± 34.4 | 196.2 ± 59.7 | 0.37 |

Data are mean ± SD

**Table IV**

**Effect of vitamin B12 supplementation on glycemic control in poorly controlled type 2 diabetic patients**

| | HbA1c (%) | | Fasting blood sugar level (mg/dL) | | Postprandial blood sugar level (mg/dL) | |
|---|---|---|---|---|---|---|
| | Baseline | 4 weeks | Baseline | 4 weeks | Baseline | 4 weeks |
| Drug group (n=20) | 10.0 ± 0.8 | 9.0 ± 0.8[a] | 157.6 ± 61.3 | 137.3 ± 44.7 | 239.2 ± 111.2 | 216.5 ± 96.4 |
| Control group (n=18) | 9.3 ± 1.0 | 9.2 ± 0.8 | 132.1 ± 29.7 | 140.6 ± 42.3 | 208.7 ± 62.3 | 222.1 ± 61.2 |
| P value (compared with control) | 0.02 | 0.43 | 0.11 | 0.81 | 0.29 | 0.83 |

[a]p<0.001 (paired t test as compared to baseline values)

ment in HbA1c in this study. For confirmation of the role of vitamin $B_{12}$ in glycemic control vitamin $B_{12}$ deficient patients further studies are needed in poorly controlled type 2 diabetic patients.

## Conclusion

Homocysteine level reduced significantly after vitamin $B_{12}$ supplementation for 4 weeks in hyperhomocysteinemic poorly controlled type 2 diabetic patients. In vitamin $B_{12}$ deficient, there was significant fall in HbA1c levels after vitamin $B_{12}$ supplementation for 4 weeks. There is role of vitamin $B_{12}$ in glycaemic control in type 2 diabetic patients.

## Ethical Issue

The study protocol was approved by the local Institutional Ethics Committee. Patients were given all the information about vitamin $B_{12}$ (methylcobalamin) including adverse effects. A written informed consent was taken from each patient and those who were willing to participate in study were enrolled in this study. All the information was recorded in case report forms. The study was registered in clinicaltrials.gov (NCT02540642).

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