

# Metformin : as First-Line Treatment for Type 2 Diabetes Prevention

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## Abstract

**Objectives:** To assess the effect of Metformin, this has multiple pharmacodynamic effects and prevention in type 2 diabetes (T2DM).

**Design:** Case - control study.

Setting: Outpatient clinics of Diabetic Endocrine Research Lab and patients reporting to medicine department of Sheth Vadilal Sarabhai General Hospital ( Smt. NHL Municipal Medical College ), Ahmedabad, Gujarat .

Participants: A total of 240 patients, 100 control group healthy normal and nondiabetic 140 study group with Type 2 Diabetes treated with Metformin and not known with a contraindication for the use of Metformin were approached, given informed consent, and entered the study.

e .Intervention : Addition of Metformin to Insulin Therapy three times a day.

**Primary Outcomes:** Vitamin B12, Folic acid , Serum Homocysteine.

**Results :** Metformin Treatment compare with control, was associated with a mean difference in Vitamin B12 -340.26 and confidence 6.71 ( 95 % confidence interval 27.53 to 40.95: P= < 0.0001) , and in Folate concentration of -6.24 and confidence 0.18 ( 95% confidence interval 0.74 to 1.1:P=0.026 ) , and an increase in Homocysteine concentration of 18.97 and confidence 0.93 ( 95% confidence interval 3.83 to 5.69 : P= <0.0001 ) . In addition, decrease Vitamin B12 and Folate could be explained by the increase in Homocysteine. The average person with type 2 DM has 3 times the normal rate of gluconeogenesis, Metformin treatment reduces this by over one – third.

**Conclusion :** Metformin use for long term has been associated with increased homocysteine level and malabsorption of Vitamin B12 which is preventable and some researchers and our findings suggests , recommend screening or prevention strategies .Metformin's efficacy, security, profile, benefic Cardio Vascular & metabolic effects, and its capacity to be associated with other antidiabetic agents makes this drug the first glucose lowering agent of choice when treating patients with T2DM.

**Key Words:** Diabetes mellitus type 2, Metformin, homocysteine, Vitamin B12 and folate.

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## Introduction

Metformin (sold as Glucophage) is an oral antidiabetic drug in the biguanide class and the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with kidney function<sup>1, 2</sup> its use in gestational diabetes

has been limited by safety concerns. The most common adverse effect of metformin is gastrointestinal irritation, including diarrhea, cramp, nausea, vomiting and increased flatulence<sup>3</sup>.

Metformin have evidence of reduced vitamin B12 absorption due to calcium-dependent ileac membrane antagonism, an effect that can be reversed with supplemental calcium. Vitamin B12 that plays a very fundamental role in DNA synthesis and neurological function, hence an essential micronutrient required for Cardiovascular and Neuro-cognitive function<sup>4,5</sup>. Clinical Vitamin B12 deficiency and biochemical has been demonstrated to be highly prevalent among patients with Type 2 diabetes mellitus.

Type 2 Diabetes Mellitus is associated with a two to four fold increase in the risk of cardiovascular disease, which cannot be fully explained by important risk factor such as hyperglycemia, hypertension and dyslipidemia<sup>6</sup>. It also appears that Diabetes interact with risk factor to increase more risk of cardiovascular disease<sup>7</sup>. Hyperhomocysteinemia is a independent cardiovascular risk factor, specially in diabetic patient<sup>8</sup>. For prevention of cardiovascular events in patients with Type 2 diabetes in addition for control of type 2 diabetes, identification and treatment of risk factor, such as hyperhomocysteinemia is critical<sup>7</sup>.

It is well known that Metformin by decreasing plasma folate and Vitamin B12 levels can increase Serum homocysteine levels<sup>7</sup>. But data on this issues are sparse and conflicting<sup>7,8,9,10</sup>.

In view of this consideration, the aim of the study is evaluating Metformin for the prevention in type 2 diabetes mellitus.

## Materials & Methods

This study included total 240 patients, 100 control group healthy patient and 140 study group with Type 2 diabetes Mellitus treated with Metformin, these patients have been referred to diabetic research laboratory and medicine department of Smt.N.H.L. Medical College, Ahmedabad, Gujarat. All patients gave informed voluntary consent to participate in the study. The study was approved by the ethic committee of Smt. N.H.L. Medical College.

We aimed to include the patient with Type 2 diabetes mellitus between 35 and 75 yrs of age during the study period from November 2012 to Dec 2016 and who had received a diagnosis of diabetes after 25 yrs of age, had never had an episode of keto-acidosis, and whose blood glucose lowering treatment had previously consisted of oral agents but now exclusive consist of insulin or insulin and Metformin. We excluded pregnant women and women trying to become pregnant and other serious medical or psychiatric disease. Patients were randomized into 2 groups trial and control, Trial group treated initially with 850 mg Metformin daily.

Doses of Metformin based on results of monthly Plasma glucose, as need be increased to 2000 mg daily. Whereas in control group 100 patients were non diabetic without any disease and healthy normal. Exclusion criteria were intolerance of Metformin or drugs which effect plasma homocysteine levels in duration of study. Following Laboratory investigations were done in study and control group. Vitamin B12 by micro particle enzyme intrinsic factor assay, Folic acid by iron capture technology and glucose by Hexokinase, Serum homocysteine was determined by Fluorescence Polarization Immuno acid. All blood specimens were drawn at 0800 hrs after 12 hrs fast.

The normal level of Vitamin B12 are 208-963.5 pg/ml and folate is 7.2-15.4 ng/ml and below the normal range of this parameters is considered to be deficiency respectively<sup>7,9</sup>. The normal level of Serum Homocysteine are between 3.36–20.44  $\mu\text{mol/l}$ . Serum homocysteine level of 20.44  $\mu\text{mol/l}$  or more is considered to be hyperhomocysteinemia<sup>6</sup>.

The data were analyzed using SPSS version 11 and P value less than 0.05 and 0.001 were considered to be statistically significant and highly significant respectively. Difference between mean Serum homocysteine levels in groups were assayed by student t- test and paired t- test. Pearson correlation test were applied to test correlation.

## Result

In final analysis, there were 240 Indian adults,  $\geq 35$  to 75 years of age with Type 2 Diabetes using Metformin (male 92 and female 48), 100 adults normal healthy in same age group (54 male and 46

female ). During Metformin treatment homocysteine increased, mean serum homocysteine 29.79  $\mu\text{mol/l}$  with standard deviation 5.06 was compared with 12.02 $\mu\text{mol/l}$  to 3.79  $\mu\text{mol/l}$  in the control group. In the patient with Metformin in Type 2 Diabetes homocysteine level was compared in both male and female with control group. Serum homocysteine level was higher in male than female. That was corresponded by other studies (Alan et al., 2005; Passaro et al.2000)<sup>9,10</sup>. The geometric mean serum vitamin B12 concentration among those with Type 2 Diabetes taking Metformin was 132.92pg/ml with standard deviation 29.39. This was significantly lower than the geometric mean concentration in those without diabetes(Control Group) 467.2 pg/ml with

standard deviation 207.81,  $P=0.0116$  . The prevalence of Biochemical Vit B 12 deficiency was 6.4% among those taking Metformin  $\geq 1-3$  years , 4.2% among those taking Metformin  $> 3-5$  years , and 8.2% among those taking  $\geq 5 - 10$  years (  $P=0.3319$  for  $\geq 1-3$  years vs  $\geq 5 - 10$  years . Similarly in patient with Metformin related folate deficiency, mean serum folate concentration was 5.56ng/ml with standard deviation 1.71as compared with 11.06 ng/ml standard deviation 2.64 in the control group.

The demography and biological characteristics of the groups are shown in Table 1. Among Metformin users mean age was  $62.22 \pm 6.47$  years, 66% were male and 34% were female.

**Table:1 Socio demographics Profile / characteristics of study population analyzed .**

	<b>Metformin ( n=140)</b>	<b>Control ( n=100)</b>
Demographics:		
Men:Women(n:n)	92:48	54:46
Age ( years )	62.22(6.47)	50.75(11.46)
Duration of Diabetes Years	12.33(4.59)	NA
Insulin Treatment Years	8(9)	NA
Laboratory variables:		
Fasting plasma glucose(FBS)(mg/dl)	159.70(68.23)	90.81(13.01)
Post Prandial blood sugar(PP2BS) (mg/dl)	205.64(70.98)	100.33(12.54)
Vitamin B12 (pg/ml)	132.92(29.39)	467.16(207.81)
Folate (ng/ml)	5.56(1.71)	11.058(2.64)
Homocysteine ( $\mu\text{mol/l}$ )	29.79(5.06)	12.02(3.79)

\*Values are in mean and standard deviation.

Compare with control, Metformin Treatment was associated with a mean difference in Vitamin B12 -334.24 and confidence 6.71 ( 95 % confidence interval 27.53 to 40.95 :  $P = < 0.0001$  ), and in Folate concentration of -5.50 and confidence 0.18 ( 95% confidence interval 0.74 to 1.1:  $P = 0.026$  ), and an increase in Homocysteine concentration of 17.77 and confidence 0.93 ( 95% confidence interval 3.83 to 5.69 :  $P = < 0.0001$  ). Comparing the patients and controls, the levels of Serum Homocysteine were highly significantly higher among patients than controls, while vitamin B12 and folic acid level was found significantly decreased in patients than controls  $P (< 0.0001)$  for each parameter.

The effect of Metformin on the variables (serum homocysteine, folate and Vitamin B12) were re-analyzed with adjustment of age, previous Metformin treatment, duration of diabetes, gender , insulin dose and actual Metformin dose separately for each variable as well as all together, all of which did not materially change the result.

The our findings correlates and demonstrated as compare to published data ( de Jager J 2010) that ,Metformin in Patients with Type 2 diabetes on long term (>5 yrs ) lead to modest increase in Serum Homocysteine levels than patients exposed to short term (<5 yrs) and patients not exposed to Metformin: these changes were correlated . When we have calculated P value it was found to be statistically highly significant ( $p = < 0.0001$ ), and rate of significance is higher in study group than in control group.

The results and findings of our study correlates compared to published data (Wulffele at el, 2003) and which show that serum level of homocysteine in individuals with Type 2 Diabetes treated with It indicates that higher homocysteine level is observed in Type 2Diabetes treated with Metformin which is a well known risk factor for the disease of the cardiovascular system which seem to be the main cause of increased mortality in patients with Type 2 Diabetes. Metformin decreases hyperglycemia primarily by suppressing glucose production by the liver<sup>3</sup>. Works by suppressing glucose production by the liver.

Our study limitations are the smaller sample size over all and also we have a small number of female participants in comparison to males. This limitation may

cause our inability to precisely evaluate completely the role of hyperhomocysteinemia in sex. Further study with more number of patients with more female participant is needed for more accuracy.

## Conclusion

In the present study, we have observed and can evaluate and recommend on the use of metformin for the prevention of type 2 diabetes . After completing the studies, we have an idea about the levels of these investigations such as Vitamin B12, folic acid Homocysteine, in patients with type 2 diabetes mellitus with Metformin, and our data provide a strong case for routine assessment of vitamin B-12 levels during treatment with Metformin.

Patients with T2DM have increased risks of various types of cancer. Tentative evidence shows metformin may decrease the risk of cancer. A direct action of metformin on cancer cells is suspected. Metformin exhibits a strong and consistent antiproliferative action on several cancer cell lines. Our findings are similar to those obtained by De Jager J et al , (2010) and Wulffele at el, (2003) that concluded in Patients with type 2 diabetes on long term (>5 yrs ) Metformin lead to modest increase in Serum Homocysteine levels than patients exposed to short term to Metformin and patients not exposed to Metformin: these changes were correlated .This means that Metformin therapy carries a potential risk for development of vitamin B12 and folic acid deficiency but can be prevented by giving supplements.metformin modestly reduces LDL and triglyceride levels too.

The risk of developing Metformin associated vitamin B12 deficiency is greatly influenced by increasing age, Metformin dose and duration of use .Our data favours that homocysteine level is affected by both non-modifiable risk factor of atherosclerosis like age and sex and modifiable risk factors like vitamin B12 and folic acid. So, person with increasing age (age above 35 years) should comprise Vitamin B12 in their health check-up and if there is any abnormality treat the underlying cause which will help individual to stay away from CVD in upcoming days up to some extent which seem to be the main cause of increased mortality in patients treated with Metformin in Type2Diabetes.

The study highlights the necessity of checking

Vitamin B12 in patients with type 2 diabetes mellitus during Metformin treatment in order to avoid this potential adverse drug reaction and preserve the beneficial effects of Metformin.

Finally, from our study we can conclude that as Metformin is generally can be recommended as a first line treatment for type 2 diabetes mellitus, as there is a good evidence that it decreases mortality<sup>1</sup>. It works by decreasing production of glucose by the liver<sup>2</sup>. Several other groups of drugs, mostly given by mouth, may also decrease blood sugar in T2DM<sup>3</sup>.

Metformin is a cornerstone in the treatment of diabetes type 2, but make no recommendations on the detection and prevention of vitamin B12 deficiency during treatment.

**Ethical Clearance-** Took from NHLMMC IEC

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**Conflict of Interest -** Nil

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