

## Research Article



## The Effect of Metformin on Absorption of Vitamin B12, Folic acid, Iron, Albumin and Calcium in Syrian Patients

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### ABSTRACT

According to the American Diabetes Association (ADA) guidelines, metformin and lifestyle modifications are the first line therapies in the treatment of type 2 diabetes mellitus. Metformin, however, causes a reduction of vitamin B12 and folic acid concentration in blood. Therefore we studied the effect of metformin on absorption in 99 type 2 Diabetic patients (metformin group 42 patients-metformin plus sulfonylurea group 57 patients) by measuring, vitamin B12, folic acid, calcium, albumin, iron and haemoglobin concentration at baseline of our study and after 6 months (Study period) using colomiteric methods, we also measured body mass index (BMI), glycated haemoglobin (HbAc1), and creatinine concentration. The results demonstrated that treatment with metformin accompanied with a reduction of vitamin B12 absorption and low concentration of folic acid and haemoglobin and glycated haemoglobin, and there was no malabsorption of calcium, iron and albumin and there was no positive effect on body Mass Index (BMI).

**Keywords:** Metformin, Malabsorption, Vitamin B12, Folic acid, Albumin, Calcium.

### INTRODUCTION

Metformin (1.1-dimethylbiguanide hydrochloride) belongs to the biguanide class of drugs that are guanidine derivatives. It is the first-line oral antidiabetic drug for the treatment of type 2 diabetes not controlled by adequate diet, especially in overweight subjects.<sup>1</sup> Since publication of the results of the UK Prospective Diabetes Study (UKPDS) in 1998, metformin has become the most widely prescribed oral agent for the treatment of diabetes.<sup>2</sup> Despite the evidence base for the benefits of metformin, concerns remain about its side effects, including the perceived risk of lactic acidosis, gastrointestinal side effects and malabsorption of vitamin B12 which may cause low concentration of serum vitamin B12.<sup>3</sup> In recent years there was a worried from malabsorption of some nutrients in diabetic patients taking metformin. Malabsorption can lead to several diseases depending on the malabsorbed nutrient. Malabsorption of vitamin B12 causes anemia, Neuropathy and Amnesia, also malabsorption of folic acid and iron can cause anemia. Most studies revealed that Metformin therapy is associated with a higher prevalence of biochemical B12 deficiency.

The objective from this paper is to study the effect of metformin on vitamin B12, folic acid, calcium, albumin and iron absorption in type 2 diabetic patients taking metformin.

### MATERIALS AND METHODS

#### Study group (subjects)

99 diabetic type 2 patients (67 male, 32 female) were divided according to the type of treatment into two

groups: group 1: treatment with metformin only for 6 months (n= 42)

Group 2: treatment with metformin and sulphonylurea (glibenclamide) for 6 months (n=57). They were all between 30-70 years. Basic features of the patients studied are summarized in table 1.

Patients with renal failure, hepatic failure, malabsorption, anaemia, vitamin B12 deficiency, metformin allergy and history of taking any vitamin B12 supplement were excluded. Levels of serum vitamin B12, folic acid, calcium, iron, albumin and creatinine haemoglobin and glycated haemoglobin were measured after 8-12 hours fasting.

Blood samples were divided into two parts. First in a dry tube where they were centrifuged at 3500 rpm for 5-8 mins, separated and stored at -80°C until they were analysed. Second part in an ETDA tube stored at (+2-+8°C) for seven days maximum for haemoglobin and glycated haemoglobin assay. BMI was calculated.

#### Laboratory analyses

Vitamin B12 and folic acid were measured by competitive chemiluminescent enzyme immunoassay (siemens, Germany). Serum calcium, iron, albumin and creatinine levels and haemoglobin levels were measured by colorimetric methods using (medichem) kit. Glycated haemoglobin was measured by using ion exchange method (bio systems).

#### Statistical analysis

The Statistical Package for the Social Science (SPSS) version 16.0 and Microsoft Office Excel 2007 were used for the statistical analysis. Results were expressed as mean± S.D. The laboratory characteristics in the two



groups were compared by the student t-test. Spearman correlation coefficient was used to study the correlation between the characteristics. For all analysis, P-value less than  $< 0.05$  was considered statistically significant.

**Table 1:** Basic features of the patients study

Patients features	Number	Percentage
<b>Age</b>		
40-30	8	8.08%
50-41	29	29.29%
60-51	39	39.39%
70-61	23	23.23%
<b>Sex</b>		
Male	67	67.67%
Female	32	32.32%
<b>Body Mass Index</b>		
Normal weight (18.5-24.9)	4	4.04%
Over weight (25-29.9)	42	42.42%
Obese (more than 30)	53	53.53%
<b>Duration of treatment</b>		
Less than 6 months	22	22.22%
Between 6months and 2years	41	41.41%
More than 2years	36	36.36%
<b>Treatment type</b>		
Metformin	42	42.42%
Metformin with Sulphonylurea (glibenclamide)	57	57.57%
<b>Smoking</b>		
	29	29.29%

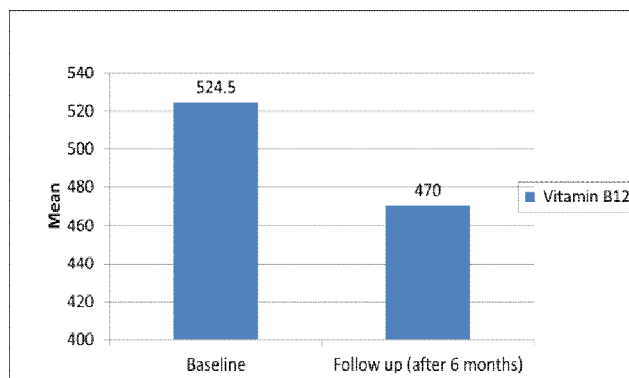
## RESULTS AND DISCUSSION

### Baseline and follow-up values for all subjects

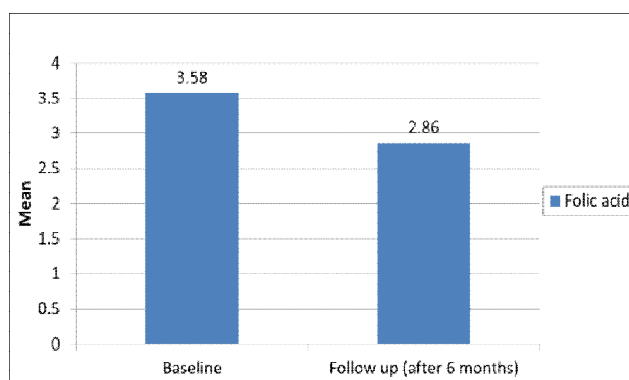
After 6 months of metformin therapy all subjects demonstrated a significant decrease in serum total vitamin B12 concentration ( $524.5 \pm 105$  vs.  $470 \pm 140$  pg/ml,  $P=0.0057$ ), figure 1 and a significant decrease in serum folic acid concentration ( $3.58 \pm 0.92$  vs.  $2.86 \pm 0.56$  ng/ml,  $P=0.0003$ ), figure 2.

No significant changes in serum calcium concentration ( $9.13 \pm 0.7$  vs.  $8.88 \pm 0.84$  mg/dl,  $P=0.06$ ), serum iron concentration ( $82.95 \pm 33.33$  vs.  $81.71 \pm 34.32$  mg/dl,  $P=0.74$ ), serum albumin concentration ( $3.97 \pm 0.4$  vs.  $4.04 \pm 0.42$  mg/dl,  $P=0.20$ ) and serum creatinine concentration ( $0.7 \pm 0.24$  vs.  $0.75 \pm 0.20$  mg/dl,  $P=0.13$ ).

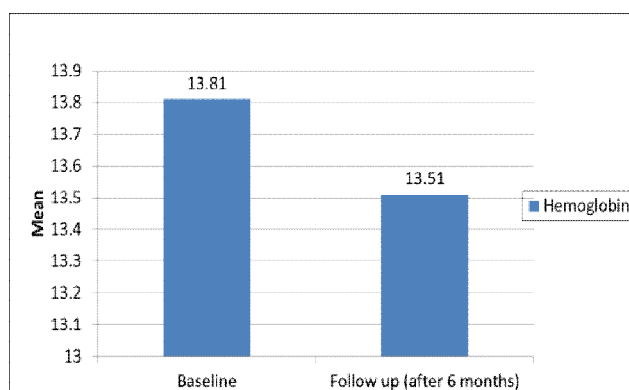
Haemoglobin concentration observed a significant decrease in all subjects taking metformin ( $13.81 \pm 1.69$  vs.  $13.51 \pm 1.53$  g/dl,  $P= 0.002$ ), figure 3 and glycated haemoglobin also ( $9.3 \pm 2.34$  vs.  $7.57 \pm 2.25\%$ ,  $P=0.008$ ), figure 4. In this study there was no positive change on BMI ( $30.62 \pm 4.09$  vs  $31.15 \pm 4.08$ ,  $P=0.051$ )



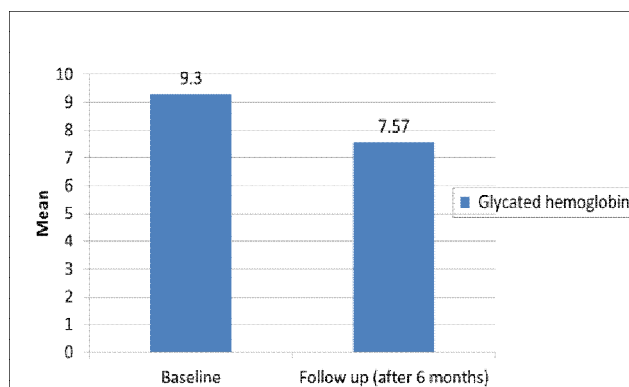
**Figure 1:** Concentration of vitaminB12 at baseline and after 6 months in all patients



**Figure 2:** Concentration of folic acid at baseline and after 6 months in all patients



**Figure 3:** Concentration of hemoglobin at baseline and after 6 months in all patients

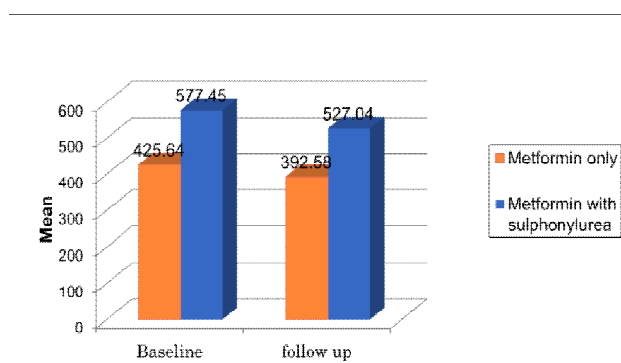


**Figure 4:** Concentration of glycated hemoglobin at baseline and after 6 months in all patients

### Correlation between types of treatment and all parameters

According to pearson coefficient there was a positive significant correlation between type of treatment (1- metformin only 2- metformin with sulphonylurea (glibenclamide) and vitamin B12 concentration at baseline and end of study respectively (P= 0.02- r=0.22, P= 0.03- r=0.21) figure 5.

There was no significant correlation between types of treatment and the other parameters.



**Figure 5:** Concentration of vitamin B12 at baseline and after 6 months according to type of treatment

### Correlation between duration of treatment and all parameters

According to pearson coefficient there was no significant correlation between duration of treatment (1- less than 6 months, 2- between 6 months and 2 years, 3- more than 2 years) and all parameters.

### DISCUSSION

In the present study, vitamin B12 and folic acid levels were found to be significantly decreased in all patients taking metformin for 6 months. This is similar to Wulfelé MG et al study which found that 16 weeks of treatment, metformin use, as compared with placebo, was associated with decreases in folate [7% P=0.024] and vitamin B12 [14% P<0.0001].<sup>4</sup> This study demonstrated no change in calcium, iron and albumin levels.

A significant decrease was observed in haemoglobin level which was similar to Marar et al., study (2011), who established that among all patients on metformin therapy, 27% were found to be anaemic but there was no correlation between haemoglobin and vitamin B12 concentration.<sup>5</sup>

A positive significant correlation was found between type of treatment (1- metformin; 2- metformin with sulphonylurea (glibenclamide) and vitamin B12 levels

which is similar to Niafar et al., study (2013) who found that Patients under long-term metformin therapy had lower vitamin B<sub>12</sub> levels than those under other hypoglycemic drugs.<sup>6</sup>

No significant correlation was found between duration of treatment (1- less than 6 months, 2- between 6 months and 2 years, 3- more than 2 years) and vitamin B12 levels this similar to Romero et al study (2012) who found No correlation between vitamin B12 plasma levels and metformin treatment time or dosage<sup>7</sup> but contrary to Marar et al., study (2011) who found a statistically significant inverse relationship between length of metformin use and vitamin B12 levels when comparing patients on metformin for five years or less to those taking it for more than five years.<sup>5</sup>

### CONCLUSION

6 months of Metformin treatment causes malabsorption of vitamin B12, reduces levels of folic acid and haemoglobin, causes no malabsorption of calcium, iron and albumin in Syrian diabetic type 2 patients.

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