

# Study of the effect of Metformin drug on folic acid levels in patients with type 2 diabetes

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## Abstract

**Objectives:** Diabetes is a major public health issue that has a significant negative impact on both communities and people. The best treatment for diabetes is metformin, which has the advantage of lowering death rates from all causes, cancer risk, and macrovascular diseases. Despite the fact that metformin is often used and extensively researched, there have only been a small number of randomized controlled studies to examine its effects on folate. In addition, it is yet unclear if short-term medication contributes to vitamin insufficiency. We hypothesize that even a brief period of metformin therapy causes folate levels to drop. However, given that metformin affects vitamins in people with type 2 diabetes, adding folate to the diet may be beneficial.

**Methods:** 30 people with type 2 diabetes were investigated. physical examination, thorough medical history, and fasting blood samples. After a 12-hour fast, all blood samples were taken.

**Results:** Our results showed that there is a direct effect of metformin on the deficiency of folic acid, as the level of folic acid decreased in the group of patients compared to the control group and it was significant . There is also an inverse relationship between folic acid and glucose in the group of patients.

**Conclusions:** Metformin lowers folic acid levels in people with type 2 diabetes. Investigations are still being done on the therapeutic relevance of these results.

**Keywords:** Levels, Patients, Type

## 1. INTRODUCTION

Metformin An oral medication called (dimethylbiguanide) is used to reduce blood glucose levels in people with non-insulin-dependent diabetes mellitus (NIDDM). 1 By increasing insulin sensitivity, it lowers the level of insulin resistance that characterizes NIDDM. Although their mechanisms of action are different, the effectiveness of glycemic control achieved with metformin and sulfonylureas is comparable. When sulfonylurea medication alone is insufficient, metformin may be administered as starting therapy or as a supplement. The usage of Galega officinalis

(also known as goat's-rue or French lilac) as a diabetes therapy in medieval Europe is where the history of biguanides may be traced. 2 In the 1920s, the active. ingredient in galega, guanidine, was used to create a number of antidiabetic drugs, including metformin and phenformin. Late in the 1950s, the two primary biguanides were first made available. Phenformin was taken out of use in clinical settings in a number

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of antidiabetic drugs, including metformin and phenformin. Late in the 1950s, the two primary biguanides were first made available. Phenformin was taken out of use in clinical settings in a number of countries when a connection to lactic acidosis was found in the late 1970s 3,4,5. This tarnished the reputation of biguanides, but metformin, which is now used in more than 90 countries, has no trouble with lactic acidosis. In Europe, it has surpassed glyburide to become the second-most often prescribed oral glucose-lowering drug. Around 40% of patients use it alone, and around 60% use it in combination with a sulfonylurea.

### Mechanism of action

Metformin's primary mechanism of action is a decrease in hepatic gluconeogenesis. [Note: High fasting blood glucose in type 2 diabetes is mostly caused by the liver's excess production of glucose.] Additionally, metformin decreases intestinal sugar absorption and enhances peripheral glucose uptake and utilization. Because metformin makes people feel less hungry, weight loss could result. The first medication of choice for type 2 diabetes, according to the ADA, is metformin. You can use metformin by itself or in conjunction with other oral medications or insulin. When metformin is taken with insulin or insulin secretagogues, hypoglycemia may result, necessitating a dosage change.

### Pharmacokinetics and fate

Orally administered metformin is well absorbed, unbound to serum proteins, and unmetabolized. The urine is used for excretion.

### Metformin and Folate Deficiency

Diabetes is a major public health issue that has a significant negative impact on both communities and people. The best treatment for diabetes is metformin, which has the advantage of lowering mortality from all causes, risk of cancer, and macrovascular disorders. However, recent observational studies have shown that long-term metformin medication raises the risk of vitamin B12 and folate deficiencies and may hasten the development of diabetic peripheral neuropathy. Despite the fact that metformin is often prescribed and extensively researched, there have only been a small number of randomized controlled trials to examine its effects on folate and vitamin B12. In addition, it is yet unclear if short-term medication contributes to vitamin insufficiency. We hypothesize that even a brief period of metformin therapy causes vitamin B12 and folate levels to drop. However, given that metformin affects vitamins in people with type 2 diabetes, supplementing with vitamin B12 alone may be more beneficial than supplementing with vitamin B12 and folate. This point of view is different from that of the majority, which tends to recommend combining vitamin B12 and folate supplements.

## MATERIALS AND METHODS

This study was conducted on 30 patients with age more than 18 years, 17 females and 13 males with type 2 diabetes mellitus, The data required for this study collected from patients include; name, age, type of antidiabetic agent. They were divided into two groups: the patients group includes 20 patients with type 2 diabetes who are taking diabetes control medication, and the second group (control) is patients with uncontrolled type 2 diabetes and includes 10 patients . This study was performed in The National University Of Science And technology in Al-Nasiriya government in winter on February 2022. 20 of the patients were controlled diabetic patient taking oral antidiabetic agent metformin as following; 4 of them receive 2000mg daily divided as two doses/day, 7 receive 1000mg/d, 5 patients taking 1700mg as two doses/day, 3 was taking 850mg/day and 6 patients was taking 500mg/day. 5 individuals had type 2 diabetes that was uncontrolled and were not taking any recommended medication. The samples were obtained by taking 5 ml of blood from each patient who had fasted overnight, placing it in EDTA and gel tubes for the HbA1c, glucose, and folic acid assays, respectively, centrifuged the gel tubes for 5 min, and then frozen the tubes at 0 C. The auto biochemistry analyzer (SMART 150 R from genoTEK), which uses a colorimetric approach, was used to measure the HbA1C and glucose levels. Folic acid levels was obtained from COBAS device from Roche which depend on Electrochemiluminescence technology.

### Statistical Analyses

The Statistical Package for the Social Sciences (SPSS) (version 20.0) application was used to do statistical computations (IBM SPSS Statistics, SPSS Inc., Chicago, Illinois, USA).

To determine whether continuous, parametric variables adhered to the normal distribution, the Anderson-Darling test was used. The mean and standard deviation of continuously distributed parametric variables with a normal distribution and no discernible outliers were presented using parametric tests; an independent two-sample student t-test was used to examine any differences between the means of the two groups.

The Pearson correlation was used to examine the correlation between the research groups.

A P value of 0.05 or less was regarded as statistically significant, and the statistical tests were accepted on the basis of the null hypothesis that there was no difference in the means of the variables.

## RESULTS

Comparison of study variables among patient and healthy control groups:

According to the findings of our study, the average level of folic acid was significantly lower in the group of type 2 diabetic patients who used metformin compared to the group of patients with uncontrolled type 2 diabetes, as shown in

table 1. The results also indicated that although not significantly different from the control group, the average level of glucose and HbA1c in the type 2 diabetes patients on metformin was lower.

**Table 1: Comparison of study variables among patient and healthy control groups.**

Variables	patients with Metformin (mean±SD)	without treatment (mean±SD)	t – test (p – value)
Age (years)	44.10±11.81	38.20 ± 8.176	0.1434†
FA (mg/ml)	6.853±5.868	17.03±1.575	<0.0001**
Glucose (mg/ml)	262.1±83.22	287.8±75.15	0.4578 †
HbA1c %	8.757±2.752	9.760±1.884	0.1023†

\*= difference of statistical significance, p≤ 0.05.

\*\*= difference of high statistical significance, p≤ 0.005.

†= difference of no statistical significance, p≥ 0.05.

**Comparison of study variables among different metformin concentration**

In Table 2, it was clear from the results of the current study that the level of folic acid was higher in the category of patients who took metformin at a concentration of 500 mg compared to the category of patients who took metformin at a concentration of 850 mg and 1000 mg, respectively, and it was significant at p value ≤ 0.05. While glucose and HbA1c were the opposite completely.

**Table 2: Comparison of study variables among different metformin concentration.**

Variables	GLU500 (mean±SD)	GLU850 (mean±SD)	GLU1000 (mean±SD)	ANOVA (p – value)
FA (mg/ml)	9.739 ± 7.998a	5.318±3.077a	4.386 ±1.919a	0.0324*
Glucose (mg/ml)	227.3 ±47.43a	270.6±104.1a	305.8 ±78.75b	0.0535†
HbA1c %	8.055 ± 1.616a	7.818±2.448b	10.67 ±3.795a	0.0257*

\*= difference of statistical significance, p≤ 0.05.

\*\*= difference of high statistical significance, p≤ 0.005.

†= difference of no statistical significance, p≥ 0.05.

Different letters means significant diefferences between the groups.

control groups:

In Table 3, it was clear from the current study that there is an inverse correlation between folic acid with glucose and HbA1c in the group of patients, on the contrary, there is a positive correlation between folic acid with glucose and HbA1c in the control group.

correlation of study variables among patient and healthy

**Table 3: correlation of study variables among patient and healthy control groups.**

	age c	age p	FA C	FA P	GLU P	GLU C	HbA1C P	HbA1C C
age c	1.00	0.20	0.77*	-0.63*	0.35	0.39	0.44	0.37
age p	0.20	1.00	0.56*	0.18	0.15	0.03	0.22	0.08
FA C	0.77*	0.56*	1.00	-0.84*	0.42	0.14	0.00	0.07
FA P	-0.63	0.18	-0.84*	1.00	-0.37	-0.51	-0.02	-0.47
GLU P	0.35	0.15	0.42	-0.37*	1.00	0.75*	0.64	0.77
GLU C	0.39	0.03	0.14	-0.51	0.75*	1.00	0.79*	0.98
HbA1C P	0.44	0.22	0.00	-0.02	0.64	0.79*	1.00	0.89
HbA1C C	0.37	0.08	0.07	-0.47	0.77	0.98	0.89	1.00

\*= difference of statistical significance,  $p \leq 0.05$

## Discussion

Our study is one of the few studies that studied the effect of metformin on the level of folic acid in patients with type 2 diabetes. Our results showed that there is a direct effect of metformin on the deficiency of folic acid, as the level of folic acid decreased in the group of patients compared to the control group and it was significant. There is also an inverse relationship between folic acid and glucose in the group of patients. Although it is unknown how metformin impacts folate status, non-diabetics have reported findings resembling ours in the past<sup>6</sup>.

In a prior study, it was shown that type 2 diabetes patients using metformin for 16 weeks had declines in blood folate and vitamin B12 of 7 and 14%, respectively<sup>7</sup>. By influencing their absorption or the metabolic process, metformin appears to lessen the use of nutrients and vitamins. Following their findings that metformin adversely affects the levels of folic acid and vitamin B12, Lijuan Xu and associates advised taking supplements of these nutrients<sup>8</sup>.

According to Mustafa Sahin and colleagues, type 2 diabetic individuals using metformin for 6 weeks saw a substantial drop in blood folate of 1.04 ng/ml (7.02%). Although our findings have been reported, it is unknown how metformin impacts the level of folate in the body<sup>9</sup>

## Compliance with Ethical Standards statements

Ethical approval :Iaqi Ministry of Health, Immam Hussein teaching hospital ,Thi-Qar, Iraqi certifies the ethical approval, Funding details (In case of Funding) :I am responsible for paying the financing, Conflict of interest :There is no conflict of interest, Informed Consent: Iaqi Ministry of Health, Immam Hussein teaching hospital ,Thi-Qar, Iraqi \ Agreed

## REFERENCES

- Tiwari, K. and Kumar, D. (2018). Recent classification of diabetes mellitus. *Himalayan Journal of Health Sciences*, 3(4), 52-57.
- Tuomilehto J. The emerging global epidemic of type 1 diabetes. *Curr Diab Rep*. 2013 Dec;13(6):795-804.
- Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ, Gross JL, Ribeiro JP, Schaan BD. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2011 May 04;305(17):1790-9.
- American Diabetes Association. Glycemic targets. *Diabetes Care* 2017 Jan; 40 (Supplement 1): S48-S56.
- Partners in Health. Chronic care integration for endemic non-communicable diseases, Chapter 7, Table 7.1. PIH, Boston, 2013.
- Carlsen SM, Følling I, Grill V, Bjerve KS, Schneede J, Refsum H. Metformin increases total serum homocysteine levels in non-diabetic male patients with coronary heart disease. *Scand J Clin Lab Invest* 1997; 57: 521-528.
- Wulffele'et al., Effects of shortterm treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebocontrolled trial. *J InternMed* 2003; 254: 455-463.
- Lijuan Xu , Zhimin Huang , Xiaoying He, Xuesi Wan, Donghong Fang, Yanbing Li; Adverse effect of metformin therapy on serum vitamin B12 and folate, *Medical Hypotheses* 81 (2013) 149-151
- Mustafa Sahin, Neslihan B. Tutuncu, Derun Ertugrul, Nedret Tanaci, Nilgun D. Guvener; Effects of metformin or rosiglitazone on serum concentrations of homocysteine, folate, and vitamin B12 in patients with type 2 diabetes mellitus; *Journal of Diabetes and Its Complications* 21 (2007) 118- 123.