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Effect of Folic Acid Supplementation on Glycemic Control in Patients with Type 2 Diabetes Mellitus.

[1]Farhan Aslam, [2]Savida Ilyas Dar, [3]Sarah Azam Shah, [4]Saira Musarrat, [5]Muhammad Adnan Umer, [6]Muaz Mubashir, [7]Lubna Meraj, [8*]Usman Wajid.

[1,2,3,6]Federal Government Poly Clinic Hospital, Islamabad, Pakistan.

[4]Garrison Medical Center, Jarrar Garrison Rawalpindi, Pakistan.

[5]District Head Quarter Hospital, Jauharabad.

[7]Department of Medicine, Benazir Bhutto Hospital, Rawalpindi Medical University, Rawalpindi, Pakistan.

[8*]University Institute of Biochemistry and Biotechnology, Pir Mehr Ali Shah Arid Agriculture University Rawalpindi.

Correspondence: wajidusman323@gmail.com.

Abstract:

Objective: To determine the effects of folic acid supplementation on biochemical indices of glycemic control i.e. HbA1c and fasting blood sugar Type 2 diabetic patients who are on oral antidiabetic agents with previously suboptimal control.

Material and Method: It was a Randomized Controlled Trial. 70 patients with Type 2 Diabetes Mellitus. The patients were divided into two groups, A and B, each containing 35 patients. Both groups were given the standard care of diabetes, including oral hypoglycemic agents and advice on diet control. However, patients in group B were given oral folic acid supplementation 5 mg daily for 12 weeks. The effectiveness of the treatments was assessed by measuring HbA1c and FBS levels at the start of the study and after 12 weeks of treatment in both groups.

Results: Total number of patients included in the study was 70. 48.6% were males, while the rest were females. Most patients (44.3%) had DM for duration of less than five years. Almost all of the patients were either on dual (metformin plus DPP4) or triple (metformin plus DPP4 plus SGLT2 inhibitor) therapy, i.e., 50% and 44.4 %, respectively. The mean age was 55.14 ± 10.44 years, while the mean BMI was 30.14 ± 3.65. A remarkably significant difference in the reduction of HbA1C was seen between the two groups with a p value of 0.001 (p=0.001).

Conclusion: The study provides evidence that folic acid supplementation is a promising adjunctive therapy for T2DM patients in lowering fasting blood glucose levels and HbA1C post-treatment.

Keywords: Diabetes Mellitus (DM), Glycosated Hemoglobin (HbA1c), Fasting Blood sugar (FBS)

Introduction:

Diabetes mellitus (DM) is a chronic metabolic disease which envelops a spectrum of insulin resistance, decreased insulin secretion as well as dysregulated glucose metabolism[1]. The overall incidence of Diabetes Mellitus (DM), a primary metabolic disease with inadequate glycemic control, has been markedly increasing. According to International Diabetic Federation (IDF), almost 415 million adults had diabetes in 2015 globally and estimates suggest a rise to 642

million by 2040.[2] In Type 2 Diabetes mellitus, initially, there is insulin resistance. Gradually, the body becomes unable to produce enough insulin from beta cells of the pancreas, resulting in hyperglycemia and leading to multiple microvascular, macrovascular, and neuropathic complications.[3] In Pakistan, the prevalence of Type 2 DM ranges from 7.6 to 11%, which is progressively increasing, and estimates suggest a rise to 15% by 2030.[4]

Despite conventional treatment with multiple oral hypoglycemic medications, many patients with Type 2 DM suffer complications of suboptimal glycemic control but remain reluctant to initiate insulin therapy, highlighting the need for adjunctive therapy.[5] In patients with DM, raised plasma homocysteine is associated with insulin resistance and hyperlipidemia, resulting in aggravation of DM by reversible pancreatic beta cell malfunction and delayed insulin synthesis.[6] Levels of plasma homocysteine are increased in patients with Diabetes Mellitus as compared to patients without diabetes.[7] Folic acid has been considered a potential adjunctive therapy among many others.it has been proposed to have an advantage in terms of improving blood sugar control as well as in decreasing the risk of complications, intensifying the effectiveness of oral antidiabetic medications, and increasing insulin sensitivity through its probable effects in lowering plasma homocysteine levels and antioxidant properties.[8]

This study was performed with meticulous care and attention to detail to assess the effectiveness of 12 weeks of oral folic acid supplementation and oral hypoglycemic drugs on Glycosylated haemoglobin (HbA1c) and fasting blood sugar in type 2 Diabetic patients with inadequate blood sugars control.

Materials and Methods:

This study was a randomized clinical trial which was conducted in the Department of Internal Medicine and Endocrinology in Federal Government Polyclinic Hospital (FGPC), Islamabad. It was conducted over a period of one year from January 2023 to January 2024. Study was started after approval from the Ethical review Board. A simple random sampling technique was used, and 70 patients were included in the study after taking informed consent. All patients who had been previously diagnosed with diabetes mellitus with poor glycemic control were included in the study. The age of study participants was between 15-80 years. Type-1 Diabetic patients, patients with Type 2 Diabetes but on insulin therapy, patients with chronic liver disease (CLD) or chronic kidney disease (CKD), all patients with chronic diarrhea, anemia due to any cause, pregnant patients, patients with history of lactation, any history of drug abuse, and patients with poor adherence to treatment as well as those lost to follow-up were excluded from the study. The patients were divided into two groups, group A and group B. Patients were included in either group randomly by lottery. There were total of 70 patients with 35 patients in each group. Both groups were given the standard care of diabetes, including oral antidiabetic agents along with advice on diet control as well as lifestyle modification. The only difference between two groups was that patients in group B were given 5 mg of folic acid orally on daily basis beyond other treatment for diabetes for a total duration of 12 weeks.

The comparison of effectiveness of the treatments was done among both groups, at the start of treatment and after a period of three months by assessing glycosylated hemoglobin (HbA1c) and fasting blood sugar (FBS) levels. A data collection form (Performa) was used to collect information regarding, gender, group assignment, total duration of Type 2 Diabetes Mellitus (T2DM), Body Mass Index (BMI), and the type of oral antidiabetic drugs used. Patient confidentiality was strictly maintained. Data analysis was performed using the Statistical Package for the Social Sciences version 26 (SPSS Inc., Chicago, USA). The Frequency and Percentage were calculated for qualitative variables, including gender and efficacy. The Mean and Standard Deviation were calculated for quantitative variables like age. Independent sample T-tests were used to measure the significance of the difference in glycemic control between the two groups. A p-value of less than 0.05 was considered statistically significant.

Results:

A total number of 70 patients were included in the trial; 48.6% were males, while the rest were females. Most patients (44.3%) had DM for a duration of less than five years. Almost all of the patients were either on dual (metformin plus DPP4) or triple (metformin plus DPP4 plus SGLT2 inhibitor) therapy, i.e., 50% and 44.4 %, respectively. The mean age was 55.14 ± 10.44 years, while the mean BMI was 30.14 ± 3.65. The details of the distribution of these variables are given in Table 1. None of these variables were found to affect the outcome significantly.

The mean value of glycosylated hemoglobin (HbA1c) and fasting blood sugar (FBS) at presentation and after 12 weeks of treatment in both groups are shown in Table 2. There was a significant difference in post-treatment values for HbA1c and FBS between the two groups ($p<0.001$).

Table 3 shows the mean reduction in glycosylated hemoglobin (HbA1C) and fasting blood sugar (FBS). There was a highly significant difference in the reduction of HbA1C ($p=0.001$ among two groups at end of treatment period. Although there was also a difference in the mean reduction in FBS between the two groups, the result was not statistically significant.

Variable	Total	Group A	Group B	p-value
Gender				0.151
• **Male**	34(48.6%)	20(57.2%)	14(40%)	
• **Female**	36(52.4%)	15(42.8%)	21(60%)	
Duration of DM				0.120
• **Less than five years**	31(44.3%)	18(51.4%)	13(37.2)	
• **5 -10 years**	24(34.3%)	13(37.2%)	11(31.4%)	
• **Greater than ten years**	15(21.4%)	4(11.4%)	11(31.4%)	
OHG drugs given				0.365
• **Metformin plus DPP4**	35(50%)	18(51.4%)	17(48.6%)	
• **Metformin plus SGLT2 inhibitor**	1(1.4%)	0	1(2.9%)	
• **Metformin plus DPP4 inhibitor plus sulfonylureas**	2(2.9%)	0	2(5.7%)	
• **Metformin plus DPP4 inhibitor plus SGLT2 inhibitor**	31(44.3%)	17(48.6%)	14(40%)	
• **Metformin**	1(1.4%)	0	1(2.9%)	
Age (Mean ± SD)	55.14 ± 10.44	52.74 ± 10.36	57.54 ± 10.11	0.874
BMI (Mean ± SD)	30.14 ± 3.65	30.93 ± 3.65	29.35 ± 3.52	0.861

Table 1: Demographic details

Variable	**Group A**	**Group B**	**p-value**
FBS pretreatment	178.46 ± 45.05	172.57 ± 39.18	0.562
FBS post-treatment	119.40 ± 27.57	100.31 ± 12.46	**0.000**
HbA1c pretreatment	9.52 ± 1.59	9.56 ± 1.71	0.933
HbA1c post-treatment	8.21 ± 0.85	7.36 ± 0.81	**0.000**

Table 2: Difference in pre- and post-treatment values between both groups.

Variable	Group A	Group B	p-value
Change in FBS	59.06 ± 34.94	72.26 ± 36.36	0.126
Change in HbA1C	1.31 ± 0.93	2.20 ± 1.18	**0.001**

Table 3: Mean changes in FBS and HbA1c between the groups

Discussion:

Diabetes mellitus is one those diseases which cause a significant burden on global health. It does not only have an impact only on the quality of life of the patients but also on their families in terms of the financial implications associated with tight glycemic control through pharmacological and non-pharmacological methods. It is of utmost importance to achieve good glycemic control to improve the morbidity as well as mortality associated with diabetes. Although the exact way by which folic acid lowers blood glucose levels is unclear, several theories have been proposed. One possibility is that the active form of homocysteine, called homocysteine thiolactone, may interfere with insulin signaling by blocking the phosphorylation of the insulin receptor and its substrates, leading to reduced glycogen synthesis and increased insulin resistance.[9] Alternatively folic acid may improve blood vessel function by reducing elevated homocysteine levels, promoting nitric oxide production, and neutralizing harmful reactive oxygen species. This may have a positive impact on glucose metabolism.[10]Folic acid supplementation, with its potential to be a low-cost and widely available intervention that could be added to the standard regime for T2DM patients, offers an optimistic outlook for future diabetes management, particularly beneficial for patients who have not achieved adequate glycemic control despite Oral hypoglycemic medications.

Our study showed that folate supplementation for 12 weeks along with oral hypoglycemic drugs in a patient with Type 2 DM with suboptimal glycemic control leads to significant improvement in HbA1c. However, findings from four studies included in the meta-analysis by Asbaghi O et al. found no significant improvement in the HbA1c of the study participants, which was attributed to a short duration of intervention ranging from 4 to 12 weeks.[11] In our study, we found that the fasting blood sugars were also significantly lowered in the treatment group with folic acid supplementations. However, the literature shows controversial results, i.e. studies done by Lind et al.[12] and Akbari et al.[13] showed that the fasting blood glucose is not lowered by folate supplementation. However, Zhao et al. showed that folate decreased fasting glucose, with an average decrease in fasting blood glucose level by upto2.7 mg%.[14]

Several studies have shown that folic acid reduces blood glucose levels by decreasing insulin resistance, which is assessed by different parameters like the Homeostatic Model of Assessment for Insulin Resistance (HOMA-IR) and insulin levels.[15] However, due to financial constraints and the non-availability of these tests in our country, we could not establish this fact alongside the role of homocysteine levels at baseline and post-treatment as a response.

This study is the first of its kind on this topic in Pakistan, and the findings of the study suggest a potential role of folic acid supplementation in achieving reasonable glycemic control. It can serve as a benchmark trial for further research to explore the potential benefits of folic acid supplementation in improving glycosylated hemoglobin (HbA1c) as well as other glucose parameters. The study also raises questions regarding optimal dosing and duration of folic acid supplementation for T2DM patients. We used a 5mg/day dosage, but it is still being determined whether higher or lower doses would be more effective. Moreover, the study's duration was around one year, and the treatment course with folic acid supplements was only 12 weeks, so it is unclear if long-term supplementation would be more effective. Future studies should address these questions and explore the potential benefits of folic acid supplementation in other patients, like those with Type 1 DM or those with pre-diabetes. Additionally, it should investigate further about

mechanism by which folic acid supplementation improves glycemic control as well as its potential interactions with other treatments.

Conclusion:

The study provides evidence that folic acid supplementation is a promising adjunctive therapy for T2DM patients in lowering fasting blood glucose levels and HbA1C post-treatment. It also highlights the need for further research on its use to fully explore potential benefits.

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