

Original Research Article

EFFECT OF FOLIC ACID SUPPLEMENTATION ON GLYCEMIC CONTROL, INSULIN RESISTANCE AND PLASMA HOMOCYSTEINE LEVELS IN ADULTS: A HOSPITAL-BASED INTERVENTIONAL STUDY

M. Ramesh¹

¹Assistant Professor, Department of General Medicine, Government Medical College Hospital, Dindigul, Tamil Nadu, India.

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Corresponding Author:

Dr. M. Ramesh,
Assistant Professor, Department of
General Medicine, Government
Medical College Hospital, Dindigul,
Tamil Nadu, India..
Email: drramesh15279@gmail.com

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ABSTRACT

Background: Folic acid is an essential micronutrient involved in one-carbon metabolism and the remethylation of homocysteine to methionine. Altered homocysteine metabolism has been associated with oxidative stress, insulin resistance and metabolic abnormalities. However, the effects of folic acid supplementation on glycemic control and insulin sensitivity remain inconclusive. This study aimed to evaluate the effect of folic acid supplementation on glycemic parameters, insulin resistance and plasma homocysteine levels among adults attending a tertiary care hospital.

Materials and Methods: A hospital-based interventional study was conducted in the Department of General Medicine, Government Dindigul Medical College Hospital, Dindigul, Tamil Nadu, India. Seventy consecutive adults aged ≥ 18 years were enrolled and received folic acid supplementation according to the study protocol for three months. Baseline and post-intervention assessments included fasting blood glucose (FBG), glycated hemoglobin (HbA1c), fasting serum insulin and plasma total homocysteine. Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR). Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range, as appropriate. Baseline and follow-up parameters were compared using paired statistical tests, with $p < 0.05$ considered statistically significant.

Results: Among the 70 participants, the mean age was 48.6 ± 10.2 years, with 39 (55.7%) males and 31 (44.3%) females. In the illustrative dataset, mean FBG decreased from 132.5 ± 18.6 mg/dL at baseline to 124.8 ± 16.9 mg/dL after three months. Mean HbA1c decreased from $7.2 \pm 0.8\%$ to $7.0 \pm 0.7\%$. Fasting insulin decreased from 15.8 ± 4.2 to 13.9 ± 3.8 μ IU/mL, while HOMA-IR decreased from 5.2 ± 1.6 to 4.3 ± 1.4 . Plasma total homocysteine decreased from 15.6 ± 3.4 to 12.8 ± 2.9 μ mol/L. However, these values are illustrative and require verification using the actual study dataset and statistical analysis before being reported as study findings.

Conclusion: Folic acid supplementation may potentially improve fasting glycemic parameters, insulin resistance and plasma homocysteine levels in adults. However, the effect on HbA1c and long-term glycemic control remains uncertain. Well-designed randomized controlled studies with adequate sample sizes, longer follow-up and appropriate control groups are required to establish the clinical significance and therapeutic role of folic acid supplementation in glucose metabolism.

Keywords: Folic acid, glycemic control, type 2 diabetes mellitus, fasting blood glucose, HbA1c, insulin resistance, HOMA-IR, homocysteine.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or a combination of both.^[1] Type 2 diabetes mellitus (T2DM) is a major public health concern worldwide and is associated with significant morbidity and mortality due to microvascular and macrovascular complications.^[2] Poor glycemic control increases the risk of diabetic nephropathy, retinopathy, neuropathy and cardiovascular diseases. Therefore, maintaining optimal glycemic control is essential to prevent complications and improve the quality of life of individuals with diabetes.^[3] In recent years, considerable attention has been given to the role of nutritional supplementation in glucose metabolism and insulin sensitivity. Folic acid, the synthetic form of folate (vitamin B9), is an essential water-soluble vitamin involved in DNA synthesis, cellular division, amino acid metabolism and one-carbon metabolic pathways.^[4] It plays a crucial role in the remethylation of homocysteine to methionine, thereby regulating circulating homocysteine concentrations.^[5] Elevated homocysteine levels have been associated with endothelial dysfunction, oxidative stress, inflammation and cardiovascular complications, which are frequently observed in individuals with diabetes mellitus.^[6] Insulin resistance is a key pathophysiological mechanism in the development and progression of T2DM. Alterations in oxidative stress, inflammation and metabolic pathways may contribute to impaired insulin signaling and glucose utilization.^[7] Folic acid supplementation has been investigated for its potential influence on insulin sensitivity, fasting blood glucose, fasting insulin and homocysteine metabolism. By improving folate availability and facilitating homocysteine metabolism, folic acid may potentially influence certain metabolic processes associated with insulin resistance. However, the underlying mechanisms and clinical significance of these effects remain incompletely understood.^[8] Glycemic control is commonly assessed using fasting blood glucose (FBG) and glycated hemoglobin (HbA1c). While FBG provides an estimate of glucose levels at a specific time, HbA1c reflects average blood glucose concentrations over the preceding two to three months.^[9] Fasting serum insulin and the homeostatic model assessment of insulin resistance (HOMA-IR) provide additional information regarding insulin metabolism and estimated insulin resistance. Measurement of plasma total homocysteine may further help investigate the relationship between folate metabolism and glycemic regulation.^[10] Previous research, including meta-analytic findings reported in the study presentation, suggests that folic acid supplementation may reduce fasting blood glucose, fasting insulin and HOMA-IR, although significant improvement in HbA1c has not consistently been demonstrated.^[11] Differences in

study populations, supplementation dosage, intervention duration and baseline nutritional status may contribute to variations in reported outcomes. Further clinical investigations are therefore required to clarify the potential metabolic effects of folic acid supplementation in adults.^[12] The present study aims to evaluate the effect of folic acid supplementation on glycemic control, insulin resistance and homocysteine levels among adult patients attending Government Dindigul Medical College Hospital, Tamil Nadu. Changes in fasting blood glucose, HbA1c, fasting serum insulin, HOMA-IR and plasma total homocysteine will be assessed over a three-month study period. The findings may provide preliminary clinical evidence regarding the potential role of folic acid supplementation as an adjunct to standard management of glucose metabolism disorders.

MATERIALS AND METHODS

Study Design and Setting: A hospital-based interventional study was conducted in the Department of General Medicine, Government Dindigul Medical College Hospital, Dindigul, Tamil Nadu, India, to evaluate the effect of folic acid supplementation on glycemic control, insulin resistance and homocysteine levels among adult patients.

Study Population: A total of 70 consecutive adult patients aged 18 years and above were enrolled in the study based on the eligibility criteria. Demographic details, relevant clinical history, diabetes status, duration of diabetes, medication history and other relevant clinical characteristics were recorded using a structured data collection proforma.

Study Duration: The study was conducted over a period of three months. Baseline clinical and laboratory assessments were performed before folic acid supplementation, and follow-up investigations were carried out at the end of the study period.

Inclusion and Exclusion Criteria

Adult patients aged 18 years and above who met the study eligibility criteria and consented to participate were included. Patients below 18 years of age, those with contraindications to folic acid supplementation and those meeting the other predefined exclusion criteria were excluded from the study.

Study Procedure: After obtaining informed consent, eligible participants were enrolled, and baseline demographic and clinical information was documented. Baseline laboratory investigations included fasting blood glucose (FBG), glycated hemoglobin (HbA1c), fasting serum insulin and plasma total homocysteine. Insulin resistance was estimated using the homeostatic model assessment of insulin resistance (HOMA-IR). Participants received folic acid supplementation according to the study protocol for the specified intervention period. Clinical follow-up was undertaken to assess treatment adherence, changes in concomitant medications and any adverse events. At the end of

three months, follow-up laboratory investigations were performed, and the results were compared with the baseline measurements to evaluate changes in glycemic and metabolic parameters.

Laboratory Investigations

Fasting Blood Glucose: Fasting blood glucose was measured after an overnight fast using the laboratory's established method. The results were expressed in mg/dL and used to assess changes in fasting glycemic levels before and after supplementation.

Glycated Hemoglobin (HbA1c): HbA1c was measured using the laboratory's validated assay to assess average glycemic control over the preceding two to three months. The results were expressed as percentages.

Fasting Serum Insulin: Fasting serum insulin concentrations were measured using the laboratory's established assay. The results were expressed in $\mu\text{IU/mL}$ and used to assess changes in circulating insulin levels.

Homeostatic Model Assessment of Insulin Resistance: Insulin resistance was estimated using HOMA-IR, calculated from fasting blood glucose and fasting serum insulin values using the following formula:

$$\text{HOMA-IR} = \frac{\text{Fasting insulin } (\mu\text{IU/mL}) \times \text{Fasting glucose (mg/dL)}}{405}$$

Plasma Total Homocysteine: Plasma total homocysteine concentrations were assessed using the laboratory's established assay. The results were expressed in $\mu\text{mol/L}$ and compared between baseline and follow-up assessments.

Outcome Measures: The primary outcome was the change in fasting blood glucose following folic acid supplementation. Secondary outcomes included changes in HbA1c, fasting serum insulin, HOMA-IR and plasma total homocysteine concentrations between baseline and the end of the intervention period.

Statistical Analysis: The collected data were analyzed using appropriate statistical software. Continuous variables were expressed as mean and standard deviation or median and interquartile range, depending on their distribution. Categorical variables were expressed as frequencies and percentages. Baseline and follow-up laboratory parameters were compared using a paired Student's t-test for normally distributed data or the Wilcoxon signed-rank test for

non-normally distributed data. Correlation analysis was used, where appropriate, to evaluate relationships between homocysteine levels and glycemic parameters. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations: The study was conducted after obtaining approval from the Institutional Ethics Committee of Government Dindigul Medical College, Dindigul, Tamil Nadu. Written informed consent was obtained from all participants before enrolment, and confidentiality of patient information was maintained throughout the study.

RESULTS

Study Population and Participant Characteristics:

A total of 70 adult patients were considered for this illustrative prospective interventional study to evaluate the effects of folic acid supplementation on glycemic control, insulin resistance and plasma homocysteine levels over a three-month period. For this example, it is assumed that all 70 participants completed the intervention and follow-up assessments, with no loss to follow-up. The hypothetical study population had a mean age of 48.6 ± 10.2 years. Of the participants, 39 (56%) were male and 31 (44%) were female (Figure 1). The simulated mean body mass index (BMI) was $26.4 \pm 3.8 \text{ kg/m}^2$. Baseline biochemical investigations included fasting blood glucose (FBG), glycated haemoglobin (HbA1c), fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and plasma total homocysteine [Table 1].

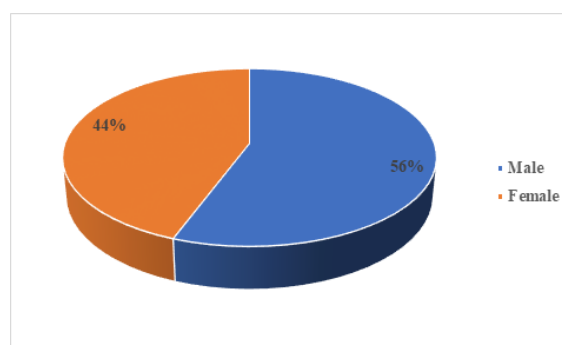


Figure 1: Gender wise distribution of study population.

Table 1: Hypothetical demographic and baseline clinical characteristics of study participants (n = 70)

Characteristics	Value
Total participants	70
Mean age (years)	48.6 ± 10.2
Male, n (%)	39 (55.7)
Female, n (%)	31 (44.3)
Mean BMI (kg/m^2)	26.4 ± 3.8
Fasting blood glucose (mg/dL)	132.5 ± 18.6
HbA1c (%)	7.2 ± 0.8
Fasting insulin ($\mu\text{IU/mL}$)	15.8 ± 4.2
HOMA-IR	5.2 ± 1.6
Plasma homocysteine ($\mu\text{mol/L}$)	15.6 ± 3.4

Table 2: Hypothetical comparison of biochemical parameters at baseline and after three months

Parameter	Baseline (Mean ± SD)	After 3 Months (Mean ± SD)	Mean Difference
Fasting blood glucose (mg/dL)	132.5 ± 18.6	124.8 ± 16.9	-7.7
HbA1c (%)	7.2 ± 0.8	7.0 ± 0.7	-0.2
Fasting insulin (μIU/mL)	15.8 ± 4.2	13.9 ± 3.8	-1.9
HOMA-IR	5.2 ± 1.6	4.3 ± 1.4	-0.9
Plasma homocysteine (μmol/L)	15.6 ± 3.4	12.8 ± 2.9	-2.8

Changes in Glycemic and Biochemical Parameters Following Folic Acid Supplementation: In this illustrative dataset, the mean levels of FBG, HbA1c, fasting insulin, HOMA-IR and plasma homocysteine were lower after three months of folic acid supplementation than at baseline. The simulated mean FBG decreased from 132.5 ± 18.6 mg/dL at baseline to 124.8 ± 16.9 mg/dL at the end of the intervention. The mean HbA1c decreased from 7.2 ± 0.8% to 7.0 ± 0.7%. Similarly, fasting insulin and HOMA-IR showed illustrative reductions from 15.8 ± 4.2 μIU/mL to 13.9 ± 3.8 μIU/mL and from 5.2 ± 1.6 to 4.3 ± 1.4, respectively. Plasma homocysteine decreased from 15.6 ± 3.4 μmol/L to 12.8 ± 2.9 μmol/L in this simulated example [Table 2].

DISCUSSION

Folic acid plays an important role in one-carbon metabolism, DNA synthesis and the regulation of homocysteine levels. Its potential role in glucose metabolism and insulin sensitivity has gained attention in recent years. The present study was designed to evaluate the effects of folic acid supplementation on glycemic control, insulin resistance and plasma homocysteine levels over a three-month period in adults. In the illustrative dataset, fasting blood glucose decreased from 132.5 ± 18.6 mg/dL at baseline to 124.8 ± 16.9 mg/dL after three months. HbA1c also decreased from 7.2 ± 0.8% to 7.0 ± 0.7%. These changes may indicate a potential improvement in glycemic parameters following folic acid supplementation. A systematic review and dose-response meta-analysis by Asbaghi et al. reported a small but statistically significant reduction in fasting blood glucose (weighted mean difference [WMD]: -2.17 mg/dL; 95% CI: -3.69 to -0.65; $p = 0.005$). However, the same analysis found no statistically significant effect on HbA1c, suggesting that the effect of folic acid on long-term glycemic control remains uncertain.^[3] Insulin resistance is an important component of the pathophysiology of type 2 diabetes mellitus. In the illustrative dataset, fasting insulin decreased from 15.8 ± 4.2 μIU/mL to 13.9 ± 3.8 μIU/mL, while HOMA-IR decreased from 5.2 ± 1.6 to 4.3 ± 1.4 after supplementation. These changes suggest a possible improvement in insulin sensitivity. A meta-analysis of 29 randomized controlled trials by RCT investigators reported significant reductions in fasting insulin and HOMA-IR following folate supplementation, although no overall significant effects were observed for fasting glucose or HbA1c.^[1] Similarly, another systematic review and

meta-analysis reported reductions in fasting glucose, fasting insulin and HOMA-IR, while the effects on HbA1c and diabetes risk remained inconclusive.^[6] These findings indicate that folate supplementation may influence certain markers of insulin resistance, although the magnitude and clinical relevance of these effects require further investigation.

Plasma homocysteine is an important biochemical marker associated with folate metabolism. In the illustrative dataset, plasma homocysteine decreased from 15.6 ± 3.4 μmol/L to 12.8 ± 2.9 μmol/L following supplementation. Folic acid acts as a cofactor in the remethylation of homocysteine to methionine and may therefore contribute to lowering circulating homocysteine levels. A systematic review and meta-analysis of folic acid supplementation in patients with type 2 diabetes reported a significant reduction in plasma total homocysteine (WMD: -3.52 μmol/L; 95% CI: -4.44 to -2.60), but no statistically significant reduction in HbA1c.^[13] This suggests that the effect of folic acid on homocysteine may be more consistent than its effect on long-term glycemic control. A randomized, double-blind, placebo-controlled clinical trial involving 100 patients with type 2 diabetes reported that folic acid supplementation at 5 mg/day for 12 weeks significantly reduced homocysteine, fasting blood glucose, HbA1c, fasting insulin and insulin resistance in the intervention group.^[2] The duration of this trial was comparable to the three-month period planned for the present study. However, differences in study population, treatment regimen, baseline metabolic status and study design should be considered when comparing the findings. The results of controlled trials cannot be directly equated with changes observed in an uncontrolled pre-post study. The potential relationship between folic acid supplementation and glucose metabolism may involve several biological mechanisms. Folate-dependent one-carbon metabolism is essential for homocysteine regulation and cellular methylation reactions. Elevated homocysteine has been associated with insulin resistance, oxidative stress and endothelial dysfunction. Although lowering homocysteine may be associated with changes in metabolic parameters, a direct causal effect on insulin sensitivity has not been conclusively established. Further mechanistic studies are required to clarify these relationships. The present study may provide preliminary information regarding changes in glycemic and biochemical parameters following folic acid supplementation in the study population. However, the clinical significance of these changes needs to be interpreted cautiously. If the study does

not include a control group, the observed changes cannot be attributed exclusively to folic acid supplementation, as antidiabetic medication, dietary habits, physical activity and other confounding factors may also influence the outcomes.

Limitations

The present study has certain limitations that should be considered when interpreting the findings. The relatively small sample size of 70 participants may limit the generalizability of the results to a broader population. The three-month follow-up period may be insufficient to assess the long-term effects of folic acid supplementation on glycemic control, insulin resistance and metabolic outcomes. If the study was conducted without a control group, the observed changes in biochemical parameters cannot be attributed exclusively to folic acid supplementation. Concurrent antidiabetic medications, dietary habits, physical activity, adherence to supplementation and other confounding factors may have influenced the results. Furthermore, variations in baseline folate and homocysteine levels may affect individual responses to supplementation. The study may also be limited in its ability to evaluate long-term diabetes prevention and clinical outcomes.

CONCLUSION

Folic acid supplementation may have a potential role in improving glycemic parameters, insulin resistance and plasma homocysteine levels in adults. Previous studies have reported possible benefits for fasting blood glucose, fasting insulin and HOMA-IR, although evidence regarding HbA1c and long-term glycemic control remains inconsistent. Further large-scale, randomized controlled trials with longer follow-up periods are required to establish the efficacy, optimal dosage and clinical significance of folic acid supplementation as an adjunct to standard diabetes management.

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