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REVIEW

Folic Acid as a Potential Vitamin in Glycemic Control: A Systematic Review

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Abstract

Purpose This systematic review aims to examine the relationship between serum folate level and folic acid supplements with glycemic control parameters (fasting blood glucose (FBG), insulin level, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and Hemoglobin A1C (HbA1c)) in adult individuals with current studies.

Methods In this study, which was designed as a systematic review, the searches were performed on Web of Science, Science Direct, Medline, Wiley, and Cochrane Library databases between April 10, 2023, and May 10, 2023, and the searches were updated between October 16, 2023, and November 14, 2023. Of the 1855 studies obtained from the screening, 17 met the criteria and were included in the systematic review. The PROSPERO system registered the study protocol (ID: CRD42023472434).

Recent Findings Although no significant correlation was found between serum folate levels and glycemic control parameters in most of the cross-sectional studies included in this systematic review, most of the randomized controlled trials showed that glycemic control parameters (FBG, insulin, HOMA-IR) decreased significantly in the intervention group receiving folic acid supplementation compared to the control group. However, study durations were short, and HbA1c needed to be evaluated in most studies. This makes it difficult to get information about the long-term effects of folic acid supplementation.

Summary More comprehensive studies should be conducted to draw more precise conclusions about the relationship between folic acid levels and folic acid supplementation with glycemic control parameters.

Keywords Folic acid · Fasting blood glucose · Insulin · HOMA-IR · HbA1c

Abbreviations

HOMA-B	Homeostasis Model Assessment of Beta-cell Function
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HbA1c	Hemoglobin A1C
HIV	Human Immunodeficiency Virus
JBI	Joanna Briggs Institute
DNA	Deoxyribonucleic acid
5-MTHF	5-Methyltetrahydrofolate
SAM	S-adenosylmethionine
T2DM	Type 2 Diabetes Mellitus
IR	Insulin Resistance
GLUT4	Glucose transporter type 4
AMPK	AMP-activated protein kinase
NF-kB	Nuclear factor kappa B
FBG	Fasting Blood Glucose
FBS	Fasting Blood Sugar
BMI	Body Mass Index
PCOS	Polycystic ovary syndrome
OAD	Oral Antidiabetic Drugs

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Introduction

Folic acid was first isolated from spinach in 1941. Since then, folic acid has been called by many different names, including vitamin B9, folate, vitamin M, and the scientific name pteroylglutamic acid [1, 2]. Although the terms folic acid and folate are frequently utilized interchangeably, folic acid, found in fortified foods and supplements, is the synthetic form of folate [3]. Foods rich in folate include animal liver, spinach, avocado, broccoli, green peas, kidney beans, and green leafy vegetables [2]. Humans cannot synthesize folate, so consuming foods rich in this vitamin meets the daily folate requirement [4]. This vitamin has many important functions in human metabolism. Folic acid is involved in one-carbon metabolism and thus provides the methyl groups necessary for biological reactions. It also has important roles in DNA synthesis, repair, and methylation [5]. Despite being so important, folic acid is a water-soluble vitamin with limited storage in the body for about 2–3 months. Folic acid deficiency can be seen in individuals of all ages where vitamin intake is inadequate and/or vitamin requirements are increased (for example, pregnant or breastfeeding). Diseases associated with folic acid insufficiency/deficiency include macrocytic anemia, neural tube defects, some types of cancer (leukemia, lymphoma, breast, colorectal, and prostate cancer), cardiovascular diseases (stroke, paralysis), and neurological diseases [4, 6, 7].

The transformation of homocysteine to methionine by the action of 5-methyltetrahydrofolate (5-MTHF) is an essential metabolic reaction of folate [8]. 5-methyltetrahydrofolate acts as a methyl donor in this pathway. After homocysteine is converted to methionine, the enzyme methionine adenosyltransferase converts some of the regenerated methionine to produce S-adenosylmethionine (SAM) [9]. Folate provides the sole carbon moiety in the synthesis pathway of S-adenosylmethionine, which influences methylation reactions and is the primary cellular methyl donor [10]. DNA, proteins, and phospholipids methylation depends on SAM, a methyl group donor. In this context, it involves many processes, from gene expression to membrane fluidity. It also plays a role in synthesizing glutathione, an important antioxidant [11]. Various enzymatic disorders in methionine metabolism or deficiency of vitamins B_6, B_{12}, and folic acid lead to high plasma total homocysteine concentrations [12]. High plasma homocysteine level or hyperhomocysteinemia has been reported to be a risk factor for coronary artery diseases and atherosclerosis [13]. Hyperhomocysteinemia is related to insulin resistance and diabetes. Homocysteine disrupts insulin signaling by altering insulin receptor phosphorylation, reducing GLUT 4 translocation, and lessening glucose uptake into the cell [14].

In an in vivo study conducted by Golbahar et al., [15] it was defined that high homocysteine could cause insulin resistance, and the researchers underlined that high homocysteine levels should be considered as a risk factor in patients with obesity and type II diabetes. Folic acid is essential in determining plasma homocysteine concentrations and is much more effective than vitamins B6 and B12 as a homocysteine-lowering agent [16]. In conclusion, folic acid supplementation decreases homocysteine levels by increasing the intracellular pool of 5-methyltetrahydrofolate, which can improve glycemic control and reduce cardiovascular events [17]. AMP-activated kinase (AMPK) plays a significant role in metabolic control. Therefore, pharmacological enhancement of AMPK activity is used to improve insulin resistance. Folic acid improves insulin resistance by increasing AMPK activity [18]. Other possible mechanisms are the antioxidant properties of folic acid; it improves endothelial dysfunction caused by high homocysteine, converts L-arginine to nitric oxide and L-citrulline, scavenges reactive oxygen species such as O_2 and peroxynitrite, maintains a combined endothelial nitric oxide synthase reaction, and reduces Nuclear factor kappa B (NF-kB) activity, which inhibits the pro-inflammatory process. All of these are involved in significantly improving the glycemic profile [19, 20]. In addition, some animal studies have found that folic acid supplementation may favor nephropathy and retinopathy, which are complications of diabetes, by declining inflammation, oxidative stress, and homocysteine levels [21, 22]. In this context, it is thought that folic acid may positively affect diabetes. However, the relationship of folic acid to glycemic control and its effects on glycemic control parameters are unclear [20, 23, 24].

On the other hand, Mangoni et al. reported that folic acid supplementation significantly reduced serum homocysteine concentrations in patients with type 2 diabetes but did not cause a significant change in the lipid and glycemic profile [25]. In light of these conflicting results in the literature, ın addition to the systematic studies in the literature [24, 26–28], it is thought that there is a need for a systematic study that evaluates the relationship between serum folic acid level and glycemic control parameters, and that includes current studies in which folic acid supplementation alone is assessed for its effect on glycemic control parameters in intervention studies. In this systematic review, we aimed to evaluate the relationship between folic acid supplementation and serum folate level and glycemic control parameters (fasting blood glucose (FBG), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), HOMA-B (Homeostasis Model Assessment of Beta Cell Function), insulin, HbA1C (Hemoglobin A1C)) in adults aged 18 and over.

Methods

The primary purpose of this systematic review is to evaluate the association of folic acid supplementation and serum folate level with glycemic control parameters. The questions aimed to be answered in the research are as follows:

1. What is the relationship of folic acid supplementation with glycemic control parameters (fasting blood glucose (FBG), HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), HOMA-B (Homeostasis Model Assessment of Beta-cell Function), insulin, HbA1C (Hemoglobin A1C))?
2. What is the relationship of serum folate level with glycemic control parameters (FBG, HOMA-IR, HOMA-B, insulin, HbA1C)?

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during study protocol and reporting [29]. In addition, the study protocol was registered in the PROSPERO system, which is the program that allows the systematic review and meta-analysis to be recorded (ID: CRD42023472434).

Search Strategy

Searches for this systematic review were carried out between April 10, 2023, and May 10, 2023. The researchers were reached by searching the Web of Science, Science Direct, Medline, Wiley, and Cochrane Library databases. In the scans ((folate OR “folic acid” OR “vitamin M” OR “vitamin B9” OR folacin OR folvite OR “pteroylglutamic Acid” OR folates OR tetrahydrofolates OR formyltetrahydrofolates OR methylTHF OR THF OR “serum folate status” OR “serum folate level” OR “folate deficiency”) AND (“glucose tolerance" OR "insulin resistance “ OR FBG OR “fasting blood sugar” OR “ serum glucose level” OR HbA1c OR “hemoglobin a1c” OR HOMA-IR OR”homeostatic model assessment" OR insulin OR "fasting blood sugar" OR FBS)) word groups are used. To reduce the number of words in Science Direct and Wiley databases, ((folate OR "folic acid") AND ("serum folate status" OR "serum folate level" OR "folate deficiency") AND ("glucose tolerance" OR "insulin resistance" OR "fasting blood glucose" OR "serum glucose level")) word groups are included. The research included in the systematic review and reference lists of previous systematic reviews and meta-analyses were checked for additional searches. The scans were updated between October 16, 2023, and November 14, 2023.

Inclusion and Exclusion Criteria

Studies eligible for this systematic review were selected according to the PICOS criteria.

P (Population)

Inclusion: Adult individuals whose serum folate levels are evaluated and/or who take folic acid supplements.

Exclusion: (1) Pregnant women and women with gestational diabetes and (2) people under the age of 18 were excluded.

I (İntervention)

Inclusion: Interventions involving supplementation of folic acid and different forms of folic acid.

Exclusion: (1) folic acid supplementation and combination with other dietary supplements, (2) maternal folic acid supplementation and maternal serum folate levels were excluded.

C (Comparison)

Comparisons of individuals without intervention (control group and placebo group), before and after intervention, according to serum folate levels.

O (Outcomes)

Fasting blood glucose, serum HOMA-IR, HOMA-B, insulin, and HbA1C were screened to evaluate glycemic control. Studies that did not include at least one of these outcomes were not included.

S (Study Designs)

Inclusion: We included randomized controlled trials to assess the beneficial effects of folic acid supplementation on glycaemic control. We also included cross-sectional and case–control studies to determine the association between folic acid and glycaemic control. The systematic review included studies conducted between 2013 and 2023 and published in English.

Exclusion: in vitro studies, case reports, animal studies, studies that did not report inclusion criteria, systematic reviews, meta-analyses, traditional reviews, and studies whose full text was inaccessible were excluded.

Study Selection

In this systematic review, a joint roadmap was established by conducting a pilot study before each stage in a joint meeting attended by the researchers to screen and select articles for data extraction to avoid the risk of potential bias. Web of Science and

Table 1 Critical evaluation checklist for JBI cross-sectional studies

Study author name and year	JBI critical appraisal checklist questions for cross-sectional studies								The quality score of studies
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	
Mahamid et al., 2018 [32]	Y	Y	U	U	Y	Y	U	Y	% 62,5 / Medium
Sivaprasad et al., 2016 [33]	Y	Y	Y	Y	N	N	Y	Y	% 75 / Medium
Kanti et al., 2020 [34]	Y	Y	Y	Y	Y	Y	Y	Y	% 100 /Good
Koo et al., 2022 [35]	Y	Y	U	U	Y	U	Y	Y	% 62,5 / Medium
Xia et al., 2018 [36]	Y	Y	Y	Y	N	N	Y	Y	% 75 / Medium

Y Yes, *N* No, *U* Unclear, *Q* Question

Medline databases were searched independently by GSA and ZK researchers. Science Direct, Wiley, and Cochrane Library databases were searched separately by AU and BA researchers, and articles were selected and collated in a joint meeting.

For this systematic review, duplicates were removed from the studies screened by four independent researchers (AU, BA, GSA, ZK); after screening according to title and abstract, the remaining studies were evaluated and selected as full text. Individual disagreements at all stages of the systematic review were resolved in consultation with the author, MGK.

Data Extraction

A data extraction tool developed by the researchers was used to obtain data in the research.

In a randomized control study, author and year of study, general characteristics of the participants (age, disease status, gender, etc.), sample size, characteristics of the groups in the study (age, body mass index (BMI)), folic acid supplement type and dose, folic acid supplementation duration, pre-intervention and post-intervention data on glycemic control parameters were obtained.

In a cross-sectional study, the author and year of the study, general characteristics of the participants (age, disease status, gender, etc.), sample size, characteristics of the groups in the study (age, BMI, sample size), serum folate level, and glycemic control parameters were obtained.

After a pilot study on how to extract the data in a joint meeting before data extraction, the data were extracted independently by the researchers (AU, BA, GSA, ZK), and the extracted data were checked and combined in a joint meeting. Individual disagreements at all stages of the systematic review were resolved in consultation with the author, MGK.

Risk of Bias (Quality) Assessment

The methodological quality of the studies included in this systematic review was evaluated according to the randomized controlled trial (13 items) [30] and cross-sectional research (8-item) checklists published by the Joanna Briggs Institute (JBI) [31]. Table 1 includes the quality assessment of cross-sectional studies, Table 2 includes the quality assessment of randomized controlled studies, and Table 3 includes the quality assessment of case–control studies. The methodological quality level of the studies included in the research was considered "poor" if less than 50% of the items were evaluated as "yes", "moderate quality" if 51–80% of the things were assessed as "yes", and "good quality" if more than 80% of the items were evaluated as "yes".

Table 2 Critical evaluation checklist for JBI randomized controlled trials

Study author name and year	Critical evaluation checklist questions for JBI randomized controlled trials													The quality score of studies
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% 76,9 /Medium
El-Khodary et al., 2022 [37]	Y	Y	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	% 76,9 /Medium
Asemi et al., 2014 [38]	U	U	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	% 61,5 /Medium
Bahmani et al., 2014 [39]	U	U	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	% 61,5 /Medium
Bahmani et al., 2018 [40]	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	%84,6/ Good
Talari et al., 2016 [41]	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	%76,9 /Medium
Qın et al., 2016 [42]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	% 92,3 /Good
Cagnacci et al., 2015 [43]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	% 100 /Good
Grigoletti et al., 2013 [44]	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	% 92,3 /Good
Satapathy et al., 2020 [45]	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	% 76,9 /Medium
Sabihi et al., 2022 [46]	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	% 92,3 /Good
Molaganbari et al. 2023 [47]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	% 92,3 /Good

Y Yes, *N* No, *U* Unclear, *NA* Not applicable, *Q* Question

Table 3 Critical evaluation checklist for JBI case–control studies

Study author name and year	Critical assessment checklist questions for JBI case–control studies										The quality score of studies
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	
Cigerli et al., 2016 [48]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	% 92,3 /Good
Yang et al. 2023 [49]	Y	Y	N	Y	Y	Y	Y	Y	N	Y	%80/ Medium

Y Yes, *N* No, *U* Unclear, *NA* Not applicable, *Q* Question

The Methodological Quality Levels of the Studies Included in the Research

Results

The PRISMA flow chart for the selection phase and systematic review of the studies is given in Fig. 1; 1855 studies were retrieved from the databases analyzed. Two hundred seventy-two articles were removed from the databases because they were duplicated. Of the remaining studies, 1557 were eliminated because they did not meet the title and abstract criteria following PRISMA guidelines. Two articles were removed because the full-text format was not available. Among the 24 studies whose full text was analyzed, 2 with different study designs and 5 with inappropriate results were excluded. Seventeen articles were included in the survey, and bias and quality assessment of these studies were performed.

Relationship Between Serum Folate Levels and Glycemic Control Parameters

This systematic review found five cross-sectional studies, ten randomized controlled trials, and two case–control studies on folic acid levels-supplements and glucose parameters.

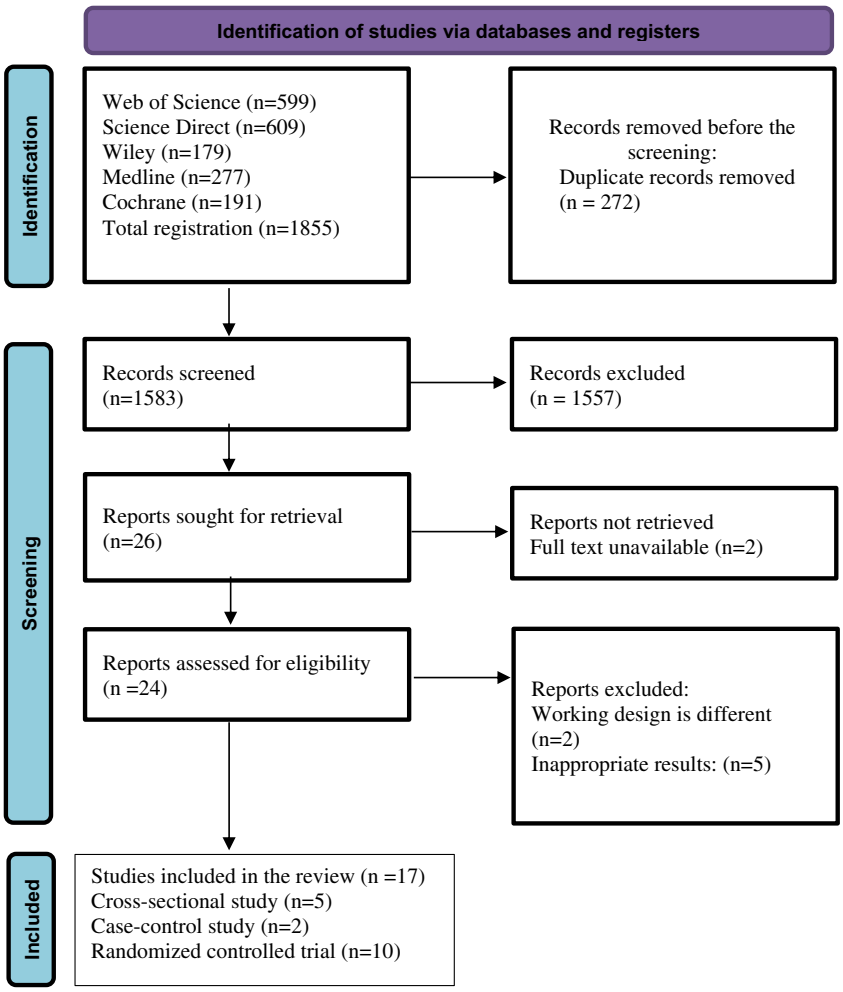


Fig. 1 PRISMA flow chart

Cross-sectional studies evaluating the relationship between folic acid levels and glucose parameters are exhibited in Table 4. Of the included cross-sectional studies, FBG was assessed in four [33–36], HOMA-IR in three [32, 34, 36], insulin level in two [32, 34], HbA1c in three [32–34], HOMA-B in one [34] and homocysteine level in two [33, 36]. While four studies included the laboratory method used to determine serum folic acid levels [33–36], one needed to include details of the laboratory method used [32].

In the study conducted by Sivaprasad et al. [33] on healthy individuals, they evaluated individuals according to the age groups of 21–40, 41–60, and > 60. While there were differences in FBG and HBA1c levels according to age groups, no distinction was defined between dietary folic acid intake and serum folic acid. Besides, no remarkable correlation was found between the general population's plasma folic acid level and FBG [33]. According to the results of univariate regression analysis in a study conducted with 84 patients aged 18 years and older diagnosed with NASH, An adverse relationship was found between folate level and HOMA-IR, HbA1c, and insulin. Still, the relationship could have been more significant [32]. Similarly, in a cross-sectional study, folic acid levels of patients diagnosed with fatty liver were classified as < 8.2 ng/mL low, 8.2–11.8 ng/mL moderate, and > 11.8 ng/mL high. Lower folic acid levels were observed more in younger men. No significant difference was observed in glycemic control parameters and homocysteine levels according to the separation of folic acid levels to be used in the study [36]. In addition, in a cross-sectional study examining the connection between folic acid levels and glycemic control parameters in individuals with diabetes, individuals with diabetes were allocated into two groups: the experimental group receiving metformin treatment and the control group not receiving pharmacological treatment. Folate levels are related to glucose-stimulated insulin secretion in drug-naive T2DM patients, independent of age and BMI. In addition, a negative correlation was determined between serum folate level and HOMA-IR in the group that did not receive pharmacological treatment [34]. In another cross-sectional study, individuals over the age of 20 were included. Individual's folic acid concentrations are classified as low, medium, and high. It has been determined that individuals with higher folic acid concentrations are older and have lower body mass index. There was no remarkable distinction in FBG according to individuals' folic acid levels [35].

In cross-sectional studies, no remarkable results were found in studies evaluating the relationship between serum folate levels and glycemic control parameters [32, 33] (except for one study [34]) and in studies comparing glycemic control parameters according to serum folic acid levels [35, 36]. The reasons for this may be the small sample sizes in some studies [32, 34, 36] and the evaluation of a small number of glycemic control parameters [33, 35, 36]. Therefore, to obtain more accurate results, studies with large sample sizes should be conducted that evaluate different glycemic control parameters directly for this relationship.

Relationship Between Folic Acid Supplementation and Glycemic Control Parameters

Randomized controlled studies and case–control studies investigating the relationship of folic acid supplementation with glucose parameters are given in Table 5. In a study conducted on overweight and obese individuals with polycystic ovary syndrome (PCOS), it was determined that the homoeostatic model assessment-beta cell function (HOMA-B) was considerably decreased in the group given 5 mg folic acid supplementation [39]. Similarly, in the study by Asemi et al. [38], participants were randomized into three groups given a daily folic acid supplement of 1 mg (folate-1), a supplement of 5 mg of folic acid (folate-5) and a placebo for eight weeks. At the end of the intervention, the group receiving 5 mg folic acid supplementation had a significantly more significant reduction in HOMA-IR level than the other groups. The decrease in insulin level was found to be greater in the Folate-5 group than in placebo [38]. In the randomized controlled study by Cagnacci et al. [43], a 15 mg/day 5-methyltetrahydrofolate (5-MTHF) supplement was given to the intervention group for three weeks. In the study, insulin and HOMA-IR values of the intervention group were considerably reduced compared to the placebo group [43]. In another study investigating the association of folic acid supplementation with glycemic control parameters, slightly overweight individuals with coronary heart disease and diabetes were randomized to the intervention group or placebo group given a daily 5 mg folic acid supplement for 12 weeks. Although serum folate levels of individuals were not assessed at the beginning of the study, no significant difference in daily dietary folic acid intake was detected between the groups. At the end of the study, individuals in the intervention group had more substantial reductions in FBG, HOMA-IR, and insulin concentration compared to the placebo group [41]. In another study, women with endometrial hyperplasia (EH) were enrolled in an intervention or placebo group, receiving 5 mg of folic acid supplements daily for 12 weeks. At the end of the intervention, fasting plasma glucose, serum insulin levels, and HOMA-IR were significantly reduced in the intervention group compared to the placebo group. It was determined that 12-week folic acid administration to individuals with EH may improve glycemic control [40]. In addition, in a randomized, controlled, double-blind clinical trial performed by El-Choudary et al. [37], subjects aged 45–75 years with Type 2 diabetes were divided into two groups given either a folic acid supplement of 5 mg daily or a placebo for 12 weeks. According to the study results,

Table 4 Cross-sectional studies evaluating the relationship between serum folate level and glycemic control parameters

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Serum Folate Level and Determination Method (DM)	Glycemic Control Parameters	Main Findings
Sivaprasad et al., 2016 [33]	Healthy adult individuals ($n=630$) Age: 21–85 years F:283 M:347	Group1 (n = 240): Age: 21–40 years BKI: 23.97 ± 0.28 kg/m^2 Group 2 (n = 184) Age: 41–60 years BKI: 25.26 ± 0.34 kg/m^2 Group 3 (n = 206): Age: > 60 years BKI: 25.21 ± 0.27 kg/m^2	Group1 Folate level: 6.3 ± 0,2 ng/ml Group 2 Folate level: 6.9 ± 0.26 ng/ml Group 3 Folate level: 6.5 ± 0.29 ng/ml DM: radioimmunoassay	**Group 1** FBG (mg/dL):96.08 ± 1.24 mg/dL HbA1c (%): 6.29 ± 0.11 Hcys (umol/L): 17.4 ± 1.3 **Group 2** FBG (mg/dL): 118.25 ± 3.62 HbA1c (%):6.27 ± 0.1 Hcys (umol/L): 16.1 ± 0.9 **Group 3:** FBG (mg/dL): 118.09 ± 2.81 HbA1c (%):7.18 ± 0.11 Hcys (umol/L): 18.0 ± 1.4	No significant relationship was determined between serum folate level and FBG and HbA1c in the general population in which the study was conducted
Mahamid et al., 2018 [32]	Individuals with Nonalcoholic steatohepatitis ($n=84$) Age: 41.12 11.18; 42 (18–74) years F:32 M:51 BKI: 28.86–2.83; 29 (22–40) kg/m^2	–	Folate level: 9,85 ± 10,90 (8,9 2,2–105) ng/mL DM: In vitro-no method details	**HOMA-IR(%):** 2,88 ± 1,06; 2,8 (1,2–5,9) **HbA1c (%):**5,38 ± 0,63; 5.4 (2–6.2) **Insulin level:** 24,71 ± 5,21; 26 (12–36,2) IU/ml	No important relationship was determined between the serum folate level of individuals and HOMA-IR, HbA1c, and insulin levels
Xia et al., 2018 [36]	Individuals with Non-alcoholic fatty liver disease ($n=200$) Individuals diagnosed by liver biopsy: Age: 46.4 ± 14.6 years F/M:37/33 BKI: 28.4 ± 5.0 kg/m^2 Individuals diagnosed using proton magnetic resonance spectroscopy: Age: 51.6 ± 14.8 years (F/M): 61/69 BKI: 26.7 ± 4.4 kg/m^2	Group 1: Low serum FA level Age: 37.5 ± 12.0 years F/M:6/16 BKI:28.8 ± 5.5 kg/m^2 Group 2: Intermediate serum FA level Age: 47.6 ± 13.5 years F/M: 13/10 BKI: 28.8 ± 5.0 kg/m^2 Group 3: High serum FA level Age: 53.0 ± 14.2 years F/M: 18/7 BKI:25.9 ± 4.8 kg/m^2	Group 1: Folate level: < 8.2 ng/mL Group 2: Folate level: 8.2–11.8 ng/mL Group 3: Folate level: > 11.8 ng/mL DM: electrochemilumines-cence immunoassay	**FBG** Group 1: 5.7 ± 1.2 mmol/L Group 2: 6.7 ± 2.2 mmol/L Group 3: 6.0 ± 1.8 mmol/L **HOMA-IR** Group 1: 3.5(2.8–5.8) Group2: 3.4(2.2–5.7) Group3: 3.0(1.8–5.2) **Hcys (umol/L)** Group 1: 11.7 (10.2–14.1) Group 2: 11.3(9.2–13.7) Group3: 9.6(7.9–12.2)	No significant difference was observed in FBG, HOMA-IR, and homocysteine levels among the groups created according to serum folate levels

Table 4 (continued)

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Serum Folate Level and Determination Method (DM)	Glycemic Control Parameters	Main Findings
Kanti et al., 2020 [34]	Individuals with diabetes mellitus ($n=249$) Age: 18–69 years F:91 M:158	Intervention group ($n=123$) Metformin treated group Age: 52.8 ± 11.6 years BMI: 31.3 ± 5.9 kg/m^2 F/M:42/81 Control group ($n=126$) Group not receiving pharmacological treatment Age: 54.4 ± 10.7 years BMI: 31.6 ± 5.8 kg/m^2 F/M: 49/77	Intervention group: Folate level: 13.4 (9.3, 19.3) nmol/L Control group: Folate level: 12.7 (9.3,22.0) nmol/L DM: electrochemiluminescence immunoassay	**HbA1c** **Intervention group:** 6.4 ± 0.9%, **Control group**: 6.3 ± 0.8% **FBG** **Intervention group:** 7.0 ± 1.6 mmol/L **Control group**: 6.7 ± 1.4 mmol/L **HOMA-IR** **Intervention group:** 3.80 (2.75, 6.16) **Control group**: 3.72 (2.12,5.36)* **HOMA-B** **Intervention group:** 105 ± 81 **Control group** 91 ± 62 **Insulin level** (pmol/L) **Intervention group:** 90.3 (65.3, 140.3) **Control group**: 83.3 (52.1, 122.9)	A negative correlation was determined between serum folate level and HOMA-IR in the group not receiving pharmacological treatment
Koo et al., 2022 [35]	Pre-menopausal women ($n=1730$) Age: ≥ 20 years 35.9 (0.3) years BKI:22.7 (0.1) kg/m^2	Group 1: Low serum FA level Age: 33.6 (0.5) years BKI: 23.0 (0.2) kg/m^2 Group 2: Intermediate serum FA level Age: 36.6 (0.5) years BKI: 22.7 (0.2) kg/m^2 Group 3: High serum FA level Age: 37.6 (0.4) years BKI: 22.2 (0.1) kg/m^2	Group 1: Folate level: < 5.6 ng/mL Group 2: Folate level: 5.7–8.6 ng/mL Group 3: Folate level: > 8.7 ng/mL DM: chemiluminescent microparticle immunoassay	**FBG** Group1: 91.6 (0.6) mg/dL Group 2: 93.1 (0.7) mg/dL Group 3: 92.5 (0.9) mg/dL	There was no remarkable distinction in FBG according to individuals' folic acid levels

F Female, *M* Male, *FA* Folic Acid, *BMI* Body Mass Index, *FBG* Fasting blood glucose, *HOMA-IR* Homeostatic Model Assessment, Insulin Resistance, *HOMA-B* Homeostasis Model Assessment of Beta-cell function, *Hcys* Homocysteine

*$p < 0.05$ There is a significant relationship between serum FA level and glycemic control parameters

[a]$p < 0.05$ There is a difference in glycemic control parameters depending on serum FA level

Table 5 Randomised controlled trials and case–control studies evaluating the relationship between folic acid supplementation and glycemic control

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Groups and Intervention Types	Intervention Time	Glycemic Control Parameters
Grigoletti et al., 2013 [44]	Individuals aged 18 and over with HIV (+) ($n=30$) Female (F) ($n=16$) Male (M) ($n=14$)	Intervention group ($n=15$) Age: 45 ± 2 years Gender (F/M): 8/7 BMI:23,9 (22,5–29,2) Control group ($n=15$) Age: 45 ± 2 years Gender (F/M): 8/7 BMI: 23,9 (23,1–27,3) kg/m^2	Intervention group: 5 mg folinic acid Control group: Placebo	Four week	**FBG** **Intervention group:** BI:99 ± 4 mg/dL AI:96 ± 2 mg/dL **Control group:** BI: 101 ± 3 mg/dL AI:95 ± 3 mg/dL **Serum Folate, ng/L** **Intervention group:** BI: 9.6 ± 0.8 ng/L AI: 24 ± 0 ng/L** **Control group:** BI: 10.4 ± 1.0 ng/L AI: 11.6 ± 1.1 ng/L
Bahmani et al., 2014 [39]	PCOS, Overweight or Obese Female individuals ($n=69$) Age:18–40 years BMI ≥ 25 kg/m^2	Intervention group 1($n=23$) Age: 25.1 ± 4.9 years BMI: 26.1 ± 6.2 kg/m^2 Intervention group 2 ($n=23$) Age:24.9 ± 5.9 years BMI: 27.6 ± 5.7 kg/m^2 Placebo ($n=23$) Age: 24.9 ± 5.09 years BMI: 29.0 ± 5.9 kg/m^2	Intervention group 1:1 mg Folic acid/day Intervention group 2: 5 mg Folic acid/day Control group: Placebo	Eight week	**HOMA-B** **Intervention group 1:** BI: 39.39 ± 3.48 AI: 40.82 ± 3.76 Change: 1.43 ± 3.45 **Intervention group 2:** BI: 51.92 ± 6.31 AI: 44.29 ± 6.82 Change: -7.63 ± 3.96[a] **Control group:** BI: 54.68 ± 4.47 AI: 68.34 ± 8.77 Change: 13.66 ± 8.04

Table 5 (continued)

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Groups and Intervention Types	Intervention Time	Glycemic Control Parameters
Asemi et al., 2014 [38]	PCOS-Obese female individuals ($n=81$) Age:18–40 years BMI $\geq$ 25 kg/m^2	Intervention group 1($n=27$) Age: 24.3 ± 5.0 years BMI: 29.3 ± 4.6 kg/m^2 Intervention group 2 ($n=27$) Age: 25.1 ± 4.5 years BMI: 27.2 ± 5.0 kg/m^2 Control group ($n=27$) Age: 24.7 ± 5.0 years BMI: 27.9 ± 4.7 kg/m^2	Intervention group 1: 1 mg Folic acid/day Intervention group 2: 5 mg Folic acid/day Control group: Placebo	Eight week	**FBG** **Intervention group 1:** BI: 85.4 ± 12.2 mg/dl AI: 81.5 ± 13.0 mg/dl Change: − 3.9 ± 12.2 mg/dl **Intervention group 2:** BI: 78.9 ± 9.1 mg/dl AI: 81.5 ± 9.2 mg/dl Change: 2.6 ± 12.3 mg/dl **Control group:** BI:66.9 ± 11.2 mg/dl AI: 71.3 ± 25.2 mg/dl Change: 4.4 ± 22.8 mg/dl **HOMA-IR** **Intervention group 1:** BI: 2.1 ± 1.0 AI: 1.9 ± 0.9 Change: − 0.2 ± 0.9[a] **Intervention group 2:** BI: 2.4 ± 1.3 AI: 2.1 ± 1.1 Change: − 0.3 ± 1.0[a] **Control group:** BY: 2.0 ± 1.1 AI: 2.7 ± 2.0 Change: 0.7 ± 2.0 **Insulin level** **Intervention group 1:** BI: 10.0 ± 3.9μIU/ml AI: 9.6 ± 3.5 μIU/ml Change: − 0.4 ± 3.5 μIU/ml **Intervention group 2:** BI: 12.1 ± 6.2 μIU/ml AI: 10.4 ± 5.7μIU/ml Change: − 1.7 ± 3.7[a] **Control group:** BI: 12.0 ± 5.5μIU/ml AI: 14.6 ± 7.0 μIU/ml Change: 2.6 ± 6.5 μIU/ml

Table 5 (continued)

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Groups and Intervention Types	Intervention Time	Glycemic Control Parameters
Cagnacci et al., 2015 [43]	Healthy non-obese postmenopausal Caucasian female individuals ($n=30$) Age:48–58 years	Intervention group ($n=15$) Age:55.9 ± 4.6 years BMI:26.6 ± 5.0 kg/m2 Control group($n=15$) Age:55.5 ± 5.1 years BMI:27.3 ± 4.5 kg/m^2	Intervention group: 15 mg/day 5-methyltetrahydrofolat (5-MTHF) Control group: Placebo	Three week	**FBG** **Intervention group:** BI: 5.04 ± 0.21 mmol/L **Control group:** BI: 5.20 ± 0.35 mmol/L **HOMA-IR** **Intervention group:** BI:2.65 ± 1.8 Change: -1.45 ± 1.3* **Control group:** BI:2.61 ± 2.0 Change: -0.04 ± 0.9 **Insulin level** **Intervention group:** BI: 78.9 ± 49.4 pmol/L Change: -15.8 ± 19.2 IU/L* **Control group:** BI: 72.2 ± 38.5 pmol/L Change: -1.5 ± 6.8 IU/L
Qın et al., 2016 [42]	Hypertensive individuals ($n=20.702$) Age:45–75 years F:11748 M:8282	Intervention group ($n=10\,016$) Age:60.0 ± 7.5 years Gender (F/M): 5874/4142 BMI: 24.9 ± 3.7 kg/m2 Control group ($n=10\,014$) Age: 59.9 ± 7.6 years Gender (F/M): 5874/4140 BMI: 24.9 ± 3.7 kg/m^2	Intervention group:10 mg/day Enalapril + 0.8 mg/day Folic acid Control group: 10 mg/day Enalapril	4.5 years	**FBG (Nmol/Litre)** **Intervention group:** BI: 5.7 ± 1.4 nmol/litre AI: 6.1 ± 1.6 nmol/litre Change: 0.5 ± 1.5 nmol/litre **Control group:** BI: 5.7 ± 1.4 nmol/litre AI: 6.1 ± 1.6 nmol/litre Change: 0.5 ± 1.5 nmol/litre **Serum folate, ng/mL** **Intervention group:** BI: 8.0 (5.6–10.4) AI: 19.8 (14.7–23.3) Change: 11.2 (5.8–16.8)[a] **Control group:** BI: 5.7 ± 1.4 nmol/litre AI: 6.1 ± 1.6 nmol/litre Change: 0.5 ± 1.5 nmol/litre

Table 5 (continued)

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Groups and Intervention Types	Intervention Time	Glycemic Control Parameters
Talari et al., 2016 [41]	Individuals with Type 2 Diabetes Mellitus ($n=60$) BMI $\geq$ 25 kg/m^2 Age: 40–85 years F = 34 M = 26	Intervention group ($n=30$): Age: 65.4 ± 11.5 years Gender (F/M): 17/13 BMI: 29.8 ± 3.8 kg/m^2 Control group($n=30$): Age: 62.1 ± 9.6 years Gender (F/M):17/13 BMI:29.8 ± 4.4 kg/m^2	Intervention group: 5 mg/day Folic acid Control group: Placebo	12 week	**FBG** **Intervention group:** BI: 106.5 ± 47.4 mg/dL AI: 104.3 ± 40.7 mg/dL Change:–2.2 ± 37.5 mg/dL[a] **Control group:** BI: 116.3 ± 41.2 mg/dL AI: 146.5 ± 73.4 mg/dL Change: 30.2 ± 65.8 mg/dL[*] HOMA-IR **Intervention group:** BI: 5.0 ± 3.3 AI: 4.4 ± 2.8 Change: –0.6 ± 2.3[a] **Control group:** BI: 5.0 ± 2.9 AI: 5.9 ± 3.6 Change: 0.9 ± 2.3[*] **Insulin level** **Intervention group:** BI: 19.0 ± 9.0μIU/ml AI: 17.0 ± 8.4μIU/ml Change: –2.0 ± 10.7 μIU/ml[a] **Control group:** BI: 17.9 ± 8.7 μIU/ml AI: 20.9 ± 10.3μIU/ml Change: 3.0 ± 7.6 μIU/ml[*] **HOMA-B** **Intervention group:** BI: 73.2 ± 51.4 AI: 66.6 ± 52.9 Change: –6.6 ± 50.2 **Control group:** BI: 59.6 ± 41.5 AI: 69.2 ± 47.0 Change: 9.6 ± 25.9

Table 5 (continued)

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Groups and Intervention Types	Intervention Time	Glycemic Control Parameters
Cigerli et al., 2016 [48] (Case Control)	Non-diabetic individuals, obese individuals, and non-diabetic individuals of normal weight ($n=454$) Age: 37.3 ± 10.1 years F:312 M:142	Case group ($n=354$): (18–55 Age) (Non-diabetic obese group BMI ≥ 30 kg/m2) Age: 37.3 ± 10.5 years Gender: F/M: 200/104 BMI:35.8 ± 6.2 kg/m^2 Control group ($n=150$) (Non-diabetic individuals of normal weight BMI:18.5-24.9 kg/m2) Age: 37.1 ± 9.5 years Gender: F/M: 112/38 BMI:22.7 ± 2.12 kg/m^2	-	Four week	HbA1c (%) Case group: 5.4 ± 0.4% Control group: 5.2 ± 0.4% FBG (FBG) Case group: 95.5 ± 8.7 mg/dL Control group: 90.6 ± 7.2 mg/dL HOMA-IR Case group: 3.4 ± 1.8 Control group: 1.7 ± 0.8 Insulin level Case group: 14.2 ± 6.7 µU/mL Control group: 7.7 ± 3.4 µU/mL Folic acid level: Case group:6.7 ± 2.6 ng/mL Control group: 7.6 ± 3.0 ng/mL
Bahmani et al., 2018 [40]	Endometrial Hyperplasia female individuals ($n=60$) Age: 35–55 years	Intervention group ($n=30$) Age: 44.7 ± 3.1 years BMI: 30.7 ± 4.6 kg/m^2 Control group ($n=30$) Age: 44.4 ± 6.5 years BMI: 30.5 ± 3.8 kg/m^2	Intervention group: 5 mg/day Folic acid Control group: Placebo		**FBG** **Intervention group:** BI: 100.6 ± 12.5 mg/dL AI: 97.2 ± 12.3 mg/dL[a] **Control group:** BI:98.4 ± 8.8 mg/dL AI: 99.6 ± 8.0 mg/dL **HOMA-IR** **Intervention group:** BI: 3.3 ± 1.4 AI: 2.7 ± 1.3[a] **Control group:** BI: 2.9 ± 1.1 AI: 3.1 ± 1.2 **Insulin level** **Intervention group:** BI: 13.4 ± 5.1 µIU/ml AI: 10.7 ± 5.0µIU/ml[a] **Control group:** BI: 12.1 ± 4.2 µIU/ml AI: 12.6 ± 4.7 µIU/ml

Table 5 (continued)

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Groups and Intervention Types	Intervention Time	Glycemic Control Parameters
El-Khodary et al., 2022 [37]	Individuals with Type 2 Diabetes Mellitus ($n=100$) Age: 45–75 years F:55 M:45	Intervention group ($n=50$) Age: 52.86 ± 9.46 years Gender (K/E):28/22 BMI: 28.34 ± 3.11 kg/m^2 Control group ($n=50$) Age: 54.46 ± 7.81 years Gender (F/M):27/23 BMI: 27.69 ± 2.64 kg/m^2	Intervention group: 5 mg/day Folic acid Control group: Placebo	12 week	**FBG** **Intervention group:** BI: 117,86 ± 16,77 mg/dl AI: 107.60 ± 10.90 mg/dl^{**a} **Control group:** BI: 120.30 ± 17.63 mg/dl AI: 116.58 ± 14.13 mg/dl **HbA1c** (%) **Intervention group:** BI: 7.57 ± 0.79 (%) AI: 6.95 ± 0.62 (%) ^{**a} **Control group:** BI: 7.56 ± 0.76 (%) AI: 7.41 ± 0.85(%) **HOMA-IR** **Intervention group:** BI: 5.70 ± 1.58 AI: 4.46 ± 1.09 ^{**a} **Control group:** BI: 5.50 ± 1.97 AI: 5.30 ± 1.68 **Insulin level** **Intervention group:** BI: 19.68 ± 5.06 µIU/ml AI: 16.98 ± 4.68 µIU/ml** **Control group:** BI: 18.98 ± 5.47 µIU/ml AI: 18.45 ± 5.44 µIU/ml

Table 5 (continued)

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Groups and Intervention Types	Intervention Time	Glycemic Control Parameters
Sabihi et al., 2022 [46]	Overweight/obese female individuals with folate deficiency and level 2/3 cervical intraepithelial neoplasia ($n=60$) Age:25–55 years BMI > 25 kg/m^2	Intervention group ($n=30$) Age: 41.0 ± 3.7 years BMI: 26.8 ± 3.3 kg/m^2 Control group ($n=30$) Age:38.5 ± 6.1 years BMI: 27.2 ± 4.6 kg/m^2	Intervention group: 5 mg/day folate Control group: Placebo (starch-containing capsule)	12 week	**FBG (µmol/L)** **Intervention group** BI: 85.0 ± 10.1 µmol/L AI: 82.9 ± 11.0 µmol/L Change: − 2.1 ± 5.3 µmol/L **Control group** BI: 85.5 ± 6.1 µmol/L AI: 85.0 ± 7.6 µmol/L Change: − 0.5 ± 6.2 µmol/L **Insulin level (µIU/mL)** **Intervention group** BI: 13.7 ± 3.4 µIU/mL AI: 10.8 ± 4.6 µIU/mL Change: − 2.9 ± 4.4 µIU/mL[a] **Control group** BI: 11.8 ± 4.6 µIU/mL AI: 11.3 ± 4.0 µIU/mL Change: − 0.5 ± 2.9 µIU/mL **HOMA-IR** **Intervention group** BI: 2.9 ± 0.8 AI: 2.2 ± 1.0 Change: − 0.6 ± 0.9[a] **Control group** BI: 2.5 ± 1.0 AI: 2.4 ± 0.9 Change: − 0.1 ± 0.7

Table 5 (continued)

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Groups and Intervention Types	Intervention Time	Glycemic Control Parameters
Molaganbari et al. 2023 [47]	Individuals with non-alcoholic fatty liver disease (NAFLD) ($n=66$) F:60 M:6	Intervention group ($n=34$): Age: 40,15 ± 15,01 years Gender (F/M): 28/6 BKI: 30,88 ± 4,43 kg/m^2 Control group ($n=32$): Age: 43,42 ± 14,59 years Gender (F/M):32/0 BKI: 31.17 ± 5 kg/m^2	Intervention group: 1 mg/gün Folic acid Control group: Placebo	Eight hafta	**FBG (mg/dl)** **Intervention group** BI: 103,62 ± 28,1 mg/dl AI: 95,8 ± 15,12 mg/dl Change: -7,82 ± 24,31 mg/dl **Control group** BI: 105,53 ± 23,53 mg/dl AI: 103,62 ± 39,65 mg/dl Change: -1,92 ± 22,55 mg/dl **Insulin level (µIU/mL)** **Intervention group** BI: 12,23 ± 5,38 µIU/mL AI: 12,79 ± 5,86 µIU/mL Change: 0,56 ± 6,25 µIU/mL[a] **Control group** BI: 10,5 ± 6,58 µIU/mL AI: 11,99 ± 6,15 µIU/mL Change: 1,5 ± 4,91 µIU/mL **HOMA-IR** **Intervention group** BI: 4,51 ± 0,73 AI: 3,36 ± 0,73 Change: -1.15 **Control group** BI: 4,33 ± 0,87 AI: 3,54 ± 1,39 Change: -0,79 ± 1,76 **Serum Folate, ng/L** **Intervention group:** BI: 8,55 ± 11,33 ng/L AI: 6,23 ± 2,57 ng/L Change: -2,33 ± 11,69 ng/L **Control group:** BI: 10,71 ± 12,71 ng/L AI: 5,06 ± 3,03 ng/L Change: -5,65 ± 12,7

Table 5 (continued)

Study Author Name, Year	Sample Size (n) and Characteristics	Group Numbers (n) and Features	Groups and Intervention Types	Intervention Time	Glycemic Control Parameters
Yang et al. 2023 [49] (Case–Control)	Individuals with and without type 2 diabetes ($n=412$) Age: 50,60 ± 12,10 years F:210 M:202 BKI: 25,71 ± 4,10 kg/m^2	Case group: Individuals with Type 2 Diabetes (n:206) Age: 50,96 ± 13,98 Gender (F/M):123/83 BKI: 26,95 (± 4,43) kg/m^2 Type 2 Diabetics with insulin resistance (IR) ($n=99$) Age: 51,40 ± 12,91 years Gender (K/E):61/38 BKI: 27,55 (24,77, 30,08) kg/m^2 Type 2 Diabetics without IR ($n=107$) Age: 50,49 ± 15,05 years Gender (K/E):62/45 BKI: 25,53 (23,26, 27,61) kg/m^2 Control group: Age: 50,24 (± 9,84) years Gender (K/E):87/119 BKI: 24,45 ± 3,29 kg/m^2			**FBG, mmom/L** **Total:** 5,52 (5,04, 6,06) mmom/L **Case group:** 5,88 (5,01, 6,93) mmom/L With IR: 6,47 (5,56, 7,66) mmom/L Non-IR: 5,51 (4,74, 6,14) mmom/L **Control group:** 5,37 (5,05, 5,64) mmom/L **Homa IR:** **Case group:** 1,67 (0,97, 2,85)* With IR: 2,91 (2,29, 4,42) Non-IR: 1,01 (0,48, 1,35) **HbA1C, n (%)** **Case group:** 9,60 (8,09, 11,10) With IR: 9,20 (7,50, 10,90) Non-IR: 10.30 (8.40, 11.60) **Serum Folate ng/ml** **Total:** 8,46 (5,87, 12,83) **Case group:** 7,07 (5,20, 10,64)* With IR: 5,92 (4,09, 9,02)[b] Non-IR: 8,16 (6,33, 13,76) **Control group:** 10.10 (6.70, 14.26)

BI Before intervention, *AI* After Intervention, *F* Female, *M* Male, *BMI* Body Mass Index, *FBG* Fasting blood glucose, *HOMA-IR* Homeostatic Model Assessment Insulin Resistance, *HIV* Human Immunodeficiency Virus, *IR* Insulin Resistance, *HOMA-B* Homeostasis Model Assessment of Beta-cell function, *PCOS* Polycystic Ovary Syndrome, *OAD* Oral antidiabetic drugs

*$p<0.05$ Significant change with intervention; **$p<0.001$significant change with intervention

[a]Significant difference compared to the control/placebo group

[b]Significant difference compared to the control/case group

3-month folic acid supplementation decreased FBG, HbA1c, insulin level, and HOMA-IR. In the placebo group, no statistically notable difference was determined in FBG, HbA1c, insulin level, and HOMA-IR [37]. In a study by Sabihi et al. [46] in overweight and obese women with folate deficiency and cervical intraepithelial neoplasia, serum insulin levels and HOMA-IR were crucially reduced in the folic acid-supplemented group (5 mg/day) compared to the placebo group.

Furthermore, folic acid supplementation was determined to cause remarkable improvements in the quantitative index of insulin sensitivity control. It has been reported that 12 weeks of folate supplementation has beneficial effects on insulin sensitivity in overweight/obese women with cervical intraepithelial neoplasia [46]. Although some studies found positive results, some found results indicating that folic acid supplementation did not significantly influence glycemic control [42, 44, 48]. In a 4-week case–control study, the case group consisted of obese individuals without diabetes, while the control group consisted of individuals with normal body weight. It was determined that obese individuals had lower serum folate levels than the control group and that these individuals had insufficient dietary folic acid intake. However, no important relationship was determined between serum folate levels and FBG, HbA1c percentage, serum insulin and HOMA-IR values in the obese experimental group without diabetes [48]. When glucose levels were examined after the application of 5 mg folinic acid for four weeks to HIV(+) individuals over 18 years of age, no significant difference was found in the intervention group and the placebo group [44]. In another study, 20.702 individuals with hypertension were randomized into two groups: 10 mg/day enalapril + 0.8 mg/day folic acid or only 10 mg/day enalapril. The intervention period lasted four and a half years. Finally, in the intervention, no substantial difference was observed in FBG change in either group. It was determined that the probability of individuals having diabetes was similar in both groups over 4.5 years [42].

In a case–control study by Yang et al., a negative relationship was determined between serum folate level and HOMA-IR level in individuals with type 2 diabetes [49]. In addition, serum folate level was found to be a factor independently affecting insulin resistance. After statistical adjustments for gender, age, length of time diabetes, drinking, and smoking history, it was determined that the negative relationship between serum folate level and HOMA-IR was not linear, and it was determined that fasting glucose and fasting insulin levels gradually increased as serum folate levels decreased in type 2 diabetes patients. At the end of the study, the researchers concluded that regular monitoring of folate levels and folic acid supplementation may be a protective approach in T2DM patients [49].

In addition, although not among the main findings of this systematic review, 8 of the ten randomized controlled trials included evaluated homocysteine levels, and these studies determined that folic acid supplementation improved serum homocysteine levels in addition to its positive effects on some glycemic control parameters [37–39, 41, 43, 44, 46, 47]. This supports the hypothesis that folic acid supplementation positively affects glycemic control parameters via homocysteine [16, 17].

Discussion

This systematic review was planned to investigate the relationship between folic acid levels and supplements to glycemic control parameters with current studies. The cross-sectional studies included in the findings found no significant relationships between folic acid level and glycemic control parameters [32, 33, 35, 36]. However, significant results were observed in some studies in the literature. For example, it has been reported that folate levels are related to insulin secretion, independent of age and BMI, in patients with Type 2 diabetes who do not receive pharmacological treatment [35], and there is a negative relation between insulin resistance and folate levels in individuals without diabetes [50].

On the other hand, some studies do not show a considerable relation between serum folate levels and glycemic control parameters [32, 36, 51]. For example, according to the results of a study in which individuals aged 18–65 years with a diagnosis of schizophrenia and schizoaffective disorder participated, no important relationship was found between serum folic acid (folate) levels and blood glucose, HbA1c, HOMA-IR, and insulin values in schizophrenia patients [52].

In experimental studies, rats with non-alcoholic steatohepatitis receiving folic acid supplementation had lower FBG [53, 54], insulin, and HOMA-IR levels compared to the control group [53]. Similarly, in experimental animals to which folic acid intervention is applied, It has been shown that insulin sensitivity [55] is higher and FBG [55, 56] and HOMA-IR [50] levels are significantly lower than in the control group.

When randomized controlled studies are examined, it was observed that folic acid supplementation positively affected some glycemic control in the intervention group compared to the control group [37–41, 43, 46]. In this systematic review, studies evaluating folic acid supplementation and positively influencing glycemic control parameters determined that folic acid supplementation was at least 5 mg/day [37–41, 43, 46]. In the study by Quin et al. [42], no remarkable difference was observed in FBG change in the intervention and control groups. However, the study had a long folic acid intervention period of 4.5 years. In addition, it was observed that the probability of diabetes in individuals in both groups was similar within a four-and-a-half-year period. The sample size of this study is large, and the follow-up period is extended. Still, folic acid supplementation remains relatively low compared to intervention studies that found significant reductions in glycemic control parameters [42].

Similarly, a study conducted eight weeks in non-alcoholic fatty liver patients determined that daily 1 mg folic acid supplementation did not significantly change FBG, HOMA IR, insülin, and serum folate levels. In this study, a positive effect depending on the amount may not have been observed [47]. In the study of Grigoletti et al., no substantial difference was determined between the intervention group administered 5 mg folinic acid and the placebo group. This may be due to using a different form of folic acid, the study's small sample size, and a specific group's coverage [44]. However, in a meta-analysis of randomized controlled trials of folic acid supplementation compared with placebo, folic acid supplementation reduced fasting insulin and HOMA-IR but had no influence on FBG or HbA1c. This meta-analysis determined that folic acid supplementation may be favorable for reducing glucose homeostasis and insulin resistance. Still, insufficient data can definitively assess its effect on developing type 2 diabetes [57]. A meta-analysis study including four randomized controlled trials found that the impact of folic acid supplementation on HbA1c levels in individuals with type 2 diabetes was insignificant [28]. Another meta-analysis study, including 24 randomized controlled trials, found that folic acid supplementation remarkably decreased FBG and fasting insulin. HOMA-IR levels in adults, but the reductions were minimal, and the same effect was not valid for HBA1c levels. In this context, it was concluded that there are question marks regarding whether folic acid supplementation can be clinically applied to adults with Type 2 diabetes [24]. As in this systematic review, other meta-analyses also found that folic acid supplementation positively affected some glycemic control parameters while others did not [28, 57]. One of the reasons for this may be that each study evaluated different glycemic control parameters. In particular, assessing HbA1c to consider the long-term effects of folic acid supplementation on glycemic control is substantial. Additionally, evaluating HbA1c and other glycemic control parameters such as FBG, insulin, and Homa-IR may provide more accurate results. However, most studies did not evaluate HbA1c [38–41, 43, 46] and assessed a small number of glycemic control parameters [39, 44].

A study of Chinese adults discovered that low folate concentrations and high homocysteine in serum were associated with an increased risk of developing type 2 diabetes. This study highlights the genetic relationship between low serum folate levels and type 2 diabetes [58]. In another cross-sectional study, erythrocyte folate level was positively associated with metabolic syndrome and some of its components in children and adults. In adults, individuals in the quartile with the highest erythrocyte folate levels were found to be two times more likely to develop metabolic syndrome than those in the lowest quartile [59]. In line with these findings in the study, it was concluded that mandatory folic acid supplementation should be considered carefully in future studies [59]. A study determined that serum folate levels decreased in patients with type 2 diabetes [60]. In a study of women with PCOS, it was found that 70% of individuals are at risk of insufficient folic acid intake [61]. In a systematic review evaluating the relationship between obesity and folate metabolism, it was determined that the serum folate level of overweight and obese individuals was lower than that of individuals with average body weight [62].

However, another point to be careful about is excessive folic acid intake. An animal study compared the metabolic effects of high and adequate folic acid intake. It has been found that excess folic acid may exacerbate fat accumulation and body weight gain, which may occur due to diet, in mice consuming a high-fat diet. It has also been found that inflammation related to impaired glucose tolerance increases in high-fat-high-folic acid-fed mice compared to mice fed high-fat-enough folic acid [63].

These studies show that serum folate levels may be associated obesity [62], with type 2 diabetes [58, 60], and metabolic syndrome [59]. Additionally, it has been found that excessive folic acid intake can have adverse effects [63]. The samples of most of the randomized controlled trials included in this systematic review were slightly overweight or obese [37–41, 46]. They were conducted in individuals with type 2 diabetes [37, 41, 49], PCOS [38, 39], and endometrial hyperplasia [40] rather than healthy individuals. In this context, positive effects of folic acid rather than adverse effects may have been observed in the samples included in this systematic review. However, it is impossible to conclude definitively because in most studies evaluating folic acid supplementation, serum folate level was not assessed separately. It should not be forgotten that uncontrolled folic acid supplementation in healthy individuals may cause excessive folic acid intake. However, in cases of problems related to glycemic control parameters in groups that may have folic acid deficiency, such as obesity, diabetes, and PCOS, it is thought that it would be more accurate first to check the serum level of folate and if there is any deficiency, to supplement folic acid accordingly and to check serum folate levels at regular intervals while supplementing.

Conclusion

Although the effect of folic acid on glycemic control is not fully known, it may have favorable effects on glycemic control through two different mechanisms. One of these is the reduction of homocysteine level of folic acid, and the other is its positive effects on inflammation. In this context, the relation between folic acid and parameters important in glycemic control (FBG, insulin Homa-IR, Homa-B, and HbA1c) was evaluated in this study. Most included cross-sectional studies did not find a significant relation between serum folate level and glycemic control parameters. When randomized controlled studies are

examined, it has been determined that folic acid supplements may positively affect FBG, serum insulin, and HOMA-IR compared to the control group in some studies.

But it is impossible to draw definitive conclusions. One of the reasons for this is that the studies were conducted with different samples. Most of the samples were slightly overweight or obese. They were conducted in individuals with type 2 diabetes, PCOS, and endometrial hyperplasia, which are groups in which folate deficiency may be seen rather than healthy individuals. Therefore, these samples may have observed positive relationships between folic acid supplementation and glycemic control parameters. However, HbA1c was not evaluated in most studies, and study periods were short. In this context, no comments can be made about the long-term effects of folic acid supplementation on glycemic control.

In groups with folic acid deficiency, such as obesity, diabetes, and PCOS, it is thought that the serum level of folate should be checked first in problems related to glycaemic control parameters. If there is any deficiency, folic acid should be supplemented accordingly. Serum folate levels should be checked periodically during supplementation.

Further research is required to understand better the pathways through which folic acid affects glycaemic control parameters and the degree of this relationship. To obtain more accurate results, long-term double-blind randomized controlled clinical trials should be conducted to evaluate the effects of folic acid supplementation on glycemic profile, FBG, serum insulin, Homa-IR, HbA1c values, and serum folate level.

Strengths and limitations

This systematic review includes some strengths and limitations. The main power of this study is the inclusion of medium- and high-quality studies, as well as a combination of both cross-sectional and randomized controlled studies. Regarding limitations, the intervention period in randomized control studies is three months or less. Therefore, the long-term effects of folic acid supplementation on the glycemic profile could not be evaluated.

Key References

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This article evaluates the causal relationship between serum folate and homocysteine and Type 2 diabetes.

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Data Availability No datasets were generated or analysed during the current study.

Compliance with Ethical Standards

Conflict of Interest AU, BA, GSA, MGK, and ZK declare no competing interests.

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