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Effects of Folate supplementation on the kidney in Streptozotocin-Induced Diabetic Rats

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A B S T R A C T

Introduction: Diabetes causes the body's metabolic balance to be in disarray, which damages organs such as the kidneys due to their high metabolic activity. Tissue damage is caused by oxidative stress and chronic inflammation. Folate may help protect against diabetes complications by reducing oxidative stress, regulating homocysteine and supporting vascular and kidney health. Thus, this study was designed to investigate the effects of daily folate supplementation on glycaemic control, oxidative stress and renal dysfunction in streptozotocin-induced diabetic rats.

Materials & Methods: Eighteen male Wistar rats were randomly divided into three groups. Diabetes was induced by a single intraperitoneal injection of streptozotocin. The first group included healthy control rats, and the second included untreated diabetic rats. The third group received daily IP injections of folate for four weeks. Fasting blood glucose was measured using a glucometer. Oxidative stress was measured in the renal tissue and serum by determining the levels of malondialdehyde (MDA) and total oxidant status (TOS), respectively. Renal histopathological changes were examined by haematoxylin and eosin staining. The data were analysed using one-way ANOVA followed by Dunnett's post hoc test. $p < 0.05$ was considered statistically significant.

Results: The results showed that folate reduced renal tissue MDA and serum triglyceride levels. Fasting blood glucose and serum TOS showed a decreasing trend, but the changes were not statistically significant. The tissue analysis showed slight improvements in kidney structure, but no full recovery was observed.

Conclusion: These data suggest that folate supplementation may provide some protection against renal injury due to diabetes. The effect on glycaemic control and full recovery of renal tissue appeared to be limited. These findings highlight the need for further studies to determine whether the combination of folate with other therapies could improve glycaemic control and promote tissue repair more effectively.

Keywords: Diabetes, Oxidative stress, Folate, Kidney function, Malondialdehyde

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Introduction

The prevalence of diabetes has increased worldwide in the last decades and it has become a major public health problem. By 2025, it was estimated that approximately 590 million adults (about 11.1% of the world's adult population) were living with diabetes, according to the International Diabetes Federation (1). Diabetes mellitus is characterised by defective insulin secretion, insulin resistance, or both, resulting in persistent hyperglycaemia (2). Chronic hyperglycaemia disrupts cellular homeostasis and progressively damages several organs, particularly the kidneys, eyes, nerves and heart (3). The kidneys are particularly vulnerable due to their high metabolic rate and rich blood supply (4). Diabetic nephropathy is a major microvascular complication of diabetes that causes progressive loss of renal function due to chronic hyperglycaemia, oxidative stress and chronic inflammation (5). The kidneys play a major role in regulating fluids, electrolytes, and waste in the body, and any dysfunction may disturb the body's internal balance (6). Insulin has an important role in the maintenance of renal function through sodium reabsorption and glomerular haemodynamics. In the context of diabetes, impaired insulin signalling is a major driver for the development and progression of diabetic kidney disease (7).

Oxidative stress, resulting from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defences of the body, is a major factor in the progression of diabetic nephropathy (8). In renal tissue, high levels of ROS and pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) disrupt insulin signalling through interference with insulin receptor substrate (IRS) phosphorylation resulting in a reduction of insulin sensitivity (9). These changes aggravate metabolic dysregulation, induce fibrotic remodelling, and activate stress-responsive signalling cascades, ultimately leading to structural kidney injury and progressive functional decline. In addition to its direct pathological effects, oxidative stress also affects the intrinsic antioxidant defence machinery of the kidney (10). Consequently, important antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) become less active, which reduces the ability of the kidneys to handle oxidative injury (11).

Since oxidative stress and inflammation are important mediators in the pathogenesis of diabetic nephropathy, a number of nutritional and pharmacological interventions have been investigated for the purpose of delaying or preventing renal damage. Compounds such as antioxidant vitamins, polyphenols, and enzymatic cofactors have shown promising effects in protecting kidney function by improving antioxidant defences and reducing inflammation (12,13). In particular, folate has gained interest for its important role in homocysteine metabolism and endothelial function. These effects imply that folate may prevent renal injury in diabetic subjects by reducing oxidative damage and maintaining tissue structure (14). Although folate has shown potential benefits, its precise effects on renal oxidative stress and pathology in diabetes are poorly defined. The present study aimed to investigate the possible protective role of folate by assessing oxidative stress markers, renal function indices, and pathological changes in a streptozotocin (STZ)-induced diabetic rat model.

Materials and methods

Study Design

The current experimental study was performed using a randomised controlled animal design in order to assess the protective effects of folate supplementation against renal oxidative stress and histopathological alterations in streptozotocin (STZ)-induced diabetic rats. Diabetes was induced experimentally and biochemical, oxidative stress and histological parameters were assessed after four weeks of intervention.

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Setting and Participants

Eighteen male Wistar rats (approximately 200 ± 20 g) were purchased from Royan Institute, Tehran, Iran. Animals were kept in standard laboratory conditions (temperature of 24 ± 1°C, relative humidity of 55 ± 5%, 12 h light/dark cycle, free access to food and water). A subset of the control and STZ-induced diabetic animals used in this study came from the same experimental cohort described in our previous publication (15). However, the present study focuses on folate intervention and presents findings that have not been reported previously. Diabetes was induced in overnight-fasted rats by a single intraperitoneal injection of freshly prepared streptozotocin (55 mg/kg; Sigma, USA) dissolved in cold 0.1 M citrate buffer (pH 4.5). To prevent acute hypoglycaemia after STZ administration, the rats received 5% sucrose solution in their drinking water for 24 hours. Rats with fasting blood glucose levels above 150 mg/dL after 72 hours were considered diabetic and included in the study. Folate treatment was initiated on day 7 after STZ injection (16). Animals were randomly divided into three groups: healthy control, untreated diabetic and folate treated diabetic groups. The folate-treated group received folate (15 mg/kg/day, dissolved in normal saline) by intraperitoneal injection for four consecutive weeks (17, 18).

Measurements & Validity and Reliability

Demographic and physiological measures

Body weight was measured at baseline and at the end of 4 weeks to assess body weight changes related to diabetes and folate treatment. Additionally, fasting blood glucose levels were measured using a portable glucometer to confirm diabetes induction and assess glycaemic status.

Biochemical Evaluations

The serum biochemical estimations were done for fasting blood sugar (FBS), triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), urea and creatinine (Cr). At the end of the experiment blood samples were collected by cardiac puncture, serum was separated and stored at −70°C until analysis. Commercial biochemical assay kits (Audit, Iran) were used following manufacturer's protocol. These assays are routine laboratory techniques for experimental and clinical biochemical assessments.

Oxidative Stress Markers Evaluation

The oxidative stress status was evaluated by measuring the levels of malondialdehyde (MDA) in renal tissue and total oxidant status (TOS) in serum samples. Kidney tissues were homogenised in 10% (w/v) phosphate-buffered saline (PBS, pH 7.4), then centrifuged at 1,600×g for 10 min at 4°C to obtain the supernatant for analysis. MDA levels were measured using a commercial assay kit (KushanZist, Iran; KZMA-OB) and serum TOS levels were measured using a TOS assay kit (KushanZist, Iran; KZTO-OB). These assays are validated methods for the assessment of lipid peroxidation and systemic oxidative stress in experimental models.

Histopathological Examination of Renal Tissue

To study the structural changes in the kidney due to diabetes and the possible protective role of folate, histopathological examination was performed. The right kidneys were fixed in 10% neutral buffered formalin, paraffin embedded, sectioned at 5 μm thickness and stained with haematoxylin and eosin (H&E). Light microscopy (100× magnification) of tissue sections was used to assess pathological findings including haemorrhage, tubular necrosis, inflammatory infiltration and proteinuria.

Statistical and Data Analysis

Statistical analyses were conducted using GraphPad Prism 10.3.1 (GraphPad Software, CA, USA). The Shapiro–Wilk test was employed to assess data normality. For normally distributed variables, one-way analysis of variance (ANOVA) followed by

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Dunnett's post hoc test was performed. A p-value less than 0.05 was considered statistically significant.

Results

No significant changes in body weight (194.2 ± 42.08 g) were observed following folate supplementation in diabetic rats (Figure 1).

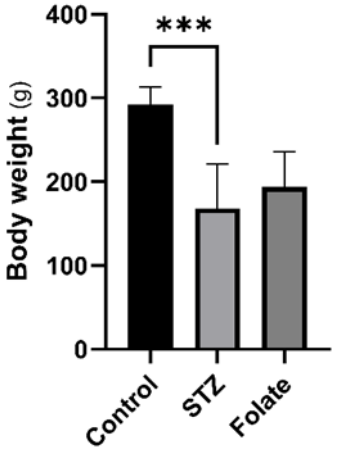

Figure 1. Body weight variations among different groups after 4 weeks of treatment. *** p-value < 0.001. Control: Non-diabetic group, STZ: diabetic group, Folate: diabetic group treated with Folate

Serum biochemical parameters are summarized in Table 1. Folate supplementation resulted in a reduction in fasting blood glucose (FBS) levels in diabetic rats; however, the change was not statistically significant. In contrast, serum triglyceride (TG) levels were significantly reduced following folate treatment (85.17 ± 23.46 vs. 138.8 ± 28.96 mg/dL, $p < 0.01$). No significant differences were observed in serum concentrations of total cholesterol, LDL-C, HDL-C, urea, or creatinine among the experimental groups.

Table 1. The Effects of Folate Supplementation on Biochemical Parameters in Streptozotocin-Induced Diabetic Rats.

Biochemical parameters	Control (n=6)	STZ (n=6)	Folate (n=6)	p value
FBS (mg/dL)	235.8 ± 67.24	562.8 ± 70.03[a**]	505.8 ± 164.2	ns
TG (mg/dL)	57.60 ± 12.95	138.8 ± 28.96[a***]	85.17 ± 23.46 [b**]	0.0052
TC (mg/dL)	67.50 ± 7.326	75.75 ± 14.15	95.00 ± 18.15	ns
LDL-C (mg/dL)	21.00 ± 5.264	36.88 ± 19.97	36.17 ± 10.87	ns
HDL-C (mg/dL)	39.50 ± 8.347	30.80 ± 2.683	50.50 ± 21.30	ns
Urea (mg/dL)	41.36 ± 2.091	66.65 ± 18.09	49.35 ± 11.36	ns
Cr (mg/dL)	0.3860 ± 0.1222	0.4900 ± 0.1013	0.4550 ± 0.1369	ns

Data are shown as mean±SD. ns; non-significant. Control: Non-diabetic group, STZ: diabetic group, Folate: diabetic group treated with folate

a. Comparison between control group and STZ group
b. Comparison between STZ group and Folate group

** $p < 0.01$
*** $p < 0.001$

Folate supplementation significantly decreased MDA levels in renal tissue (18.31 ± 7.85 µM/mg protein), restoring them toward control levels ($p < 0.001$) (Figure 2).

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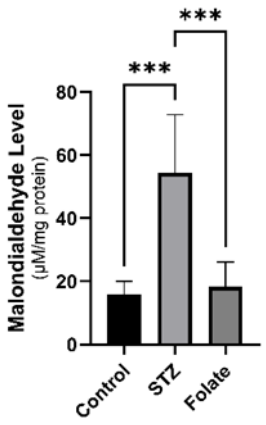

Figure 2. Levels of MDA in kidney tissue across various groups
*** p-value < 0.001. Control: Non-diabetic group, STZ: diabetic group, Folate: diabetic group treated with folate

As shown in Figure 3, serum TOS levels were considerably higher in the STZ group (40.00 ± 29.66 µmol H_2O_2 Eq/L) compared to the control group (3.43 ± 1.82 µmol H_2O_2 Eq/L), although the difference was not statistically significant. Folate supplementation reduced TOS levels to 4.03 ± 3.54 µmol H_2O_2 Eq/L; however, this reduction also did not reach statistical significance relative to the STZ group ($p = 0.07$).

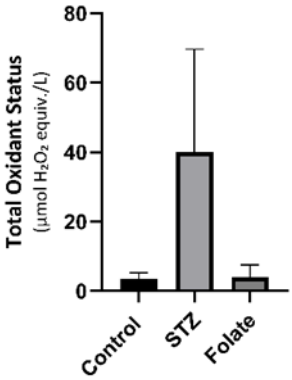

Figure 3. Total oxidant status (TOS) levels in serum of control, diabetic, and folate-treated diabetic rats
Control: Non-diabetic group, STZ: diabetic group, Folate: diabetic group treated with folate

Histological examination of the control group revealed normal renal architecture with no detectable pathological alterations (Figure 4a). In contrast, renal tissue from the STZ group exhibited multiple pathological changes, including multifocal haemorrhages, mild multifocal lymphoplasmacytic nephritis, acute tubular necrosis (ATN), and varying degrees of proteinuria, evidenced by proteinaceous casts within the tubular lumens (Figure 4b–4d). In the folate-treated group, notable histological improvements were evident, with only low-grade multifocal lymphoplasmacytic nephritis and mild proteinuria, indicating a partial protective effect of folate against STZ-induced renal injury (Figure 4e–4f).

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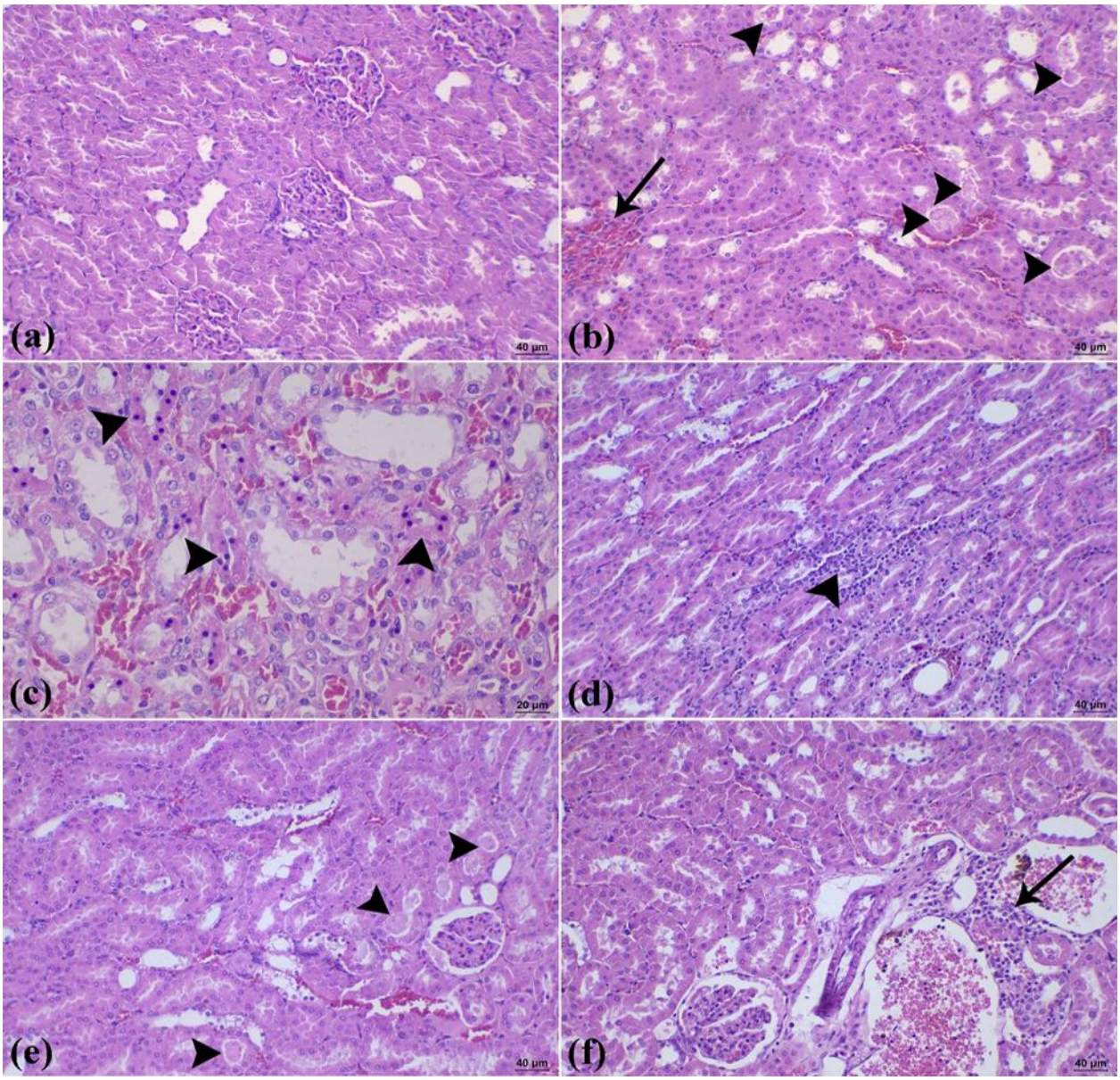

Figure 4. (a-f): Histopathological findings of kidney tissue in different groups. (a): Normal tissue in the control (non-diabetic) group. (b-d): STZ (diabetic) group. (b): haemorrhage (arrow) and proteinuria (arrowheads), (c): ATN (arrowheads), (d): focal lymphoplasmacytic nephritis (arrowhead), (e-f): Folate group. (e): proteinuria (arrowheads), (f): focal lymphoplasmacytic nephritis (arrow), H&E staining.

Discussion

Streptozotocin (STZ)-induced diabetes is reported to induce oxidative stress and profound pathological changes, especially in renal tissue. This study showed a significant increase in MDA levels in the STZ group, indicating enhanced lipid peroxidation and oxidative damage. However, folate supplementation restored MDA levels toward baseline, suggesting its potential to reduce oxidative stress. Histopathology, on the other hand, showed a partial restoration of the renal tissue integrity with some cellular disruption.

Folate is important for kidney function. The kidneys have a high concentration of folate receptors, which mediate the selective uptake of folate into renal tissue. Folate metabolism depends on a high availability of NADPH that is necessary to maintain antioxidant defences and redox homeostasis. Folate plays an important role in lowering elevated homocysteine levels by promoting its remethylation

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to methionine via methionine synthase, thereby reducing oxidative stress and inflammatory responses (19). Folate exerts anti-inflammatory effects through inhibition of NF-κB signalling, thereby limiting cytokine-driven tissue injury and reducing oxidative stress in diabetic nephropathy (20). Furthermore, folate participates in glutathione biosynthesis and regeneration, thereby elevating cellular resistance to ROS and decreasing lipid peroxidation (21).

Folate deficiency in diabetic patients has been strongly associated with the accelerated progression of diabetic nephropathy, mainly through the amplification of oxidative stress, chronic inflammation, and endothelial dysfunction. Low levels of folate disrupt redox homeostasis, leading to increased lipid peroxidation, decreased activity of antioxidant enzymes, and excess ROS production (22). Histopathological evidence further links folate deficiency with tubular injury, inflammatory infiltration, and fibrosis, all of which contribute to progressive loss of renal function (23). These findings underscore the importance of optimal folate levels in the prevention and management of diabetic kidney disease.

Our results showed that the administration of folate to STZ-induced diabetic rats significantly reduced MDA levels in renal tissue and restored them toward near-normal values, suggesting that folate has a potent antioxidant activity in preventing lipid peroxidation. These findings are in agreement with other studies that have shown folate to decrease oxidative stress and inhibit inflammation in diabetic nephropathy. In line with these findings, Ebaid et al. (2020) reported that folate supplementation improved oxidative balance in the kidneys of diabetic rats (24). Similarly, Jing et al. (2023) showed that folate ameliorated renal injury through regulation of NF-κB signalling and inhibition of M1 macrophage polarization (23). The clinical importance of folate is also reinforced by the data from the NHANES (2011–2020) survey (25), where increased circulating levels of 5-methyl-THF were associated with better renal function and less oxidative stress in diabetic subjects. Folate treatment decreased serum TOS levels towards control levels, but the effect was not statistically significant because of variability within the groups. This agrees with previous reports that oxidative stress markers are variable in diabetic models due to metabolic fluctuations (26). Importantly, to the best of our knowledge, there are no previous studies that have directly assessed TOS in diabetic models, and therefore, direct comparison is difficult.

Besides its well-known role in the metabolism of glutathione, folate supports enzymatic systems such as SOD and CAT and therefore enhances the antioxidant defence network at the molecular level (21). Critically, the dose of folate used in this study was within a physiologically safe and protective range, further supporting its potential for renal protection. Future studies should investigate the dose-dependent effects of folate on renal oxidative stress, especially regarding its long-term effect on diabetic nephropathy and the variability in oxidative stress biomarkers. At present, conflicting data are few and far between that could hint at the existence of research gaps, particularly in terms of the dose-response relationships, organ-specific mechanisms, and long-term efficacy of folate supplementation in diabetic kidney disease (27, 28). Folate deficiency is associated with higher homocysteine levels, which affect lipid metabolism by increasing the oxidation of low-density lipoprotein (LDL), promoting endothelial dysfunction, and increasing triglyceride concentrations. It also impairs the high-density lipoprotein cholesterol (HDL-C) level and aggravates the dyslipidemia (29, 30).

Deficiency of folate causes hyperhomocysteinemia (HHcy), which has adverse effects on lipid metabolism by enhancing LDL oxidation, endothelial dysfunction, and hypertriglyceridemia and reducing HDL-C levels, finally resulting in

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dyslipidemia (29, 30). In our study, folate supplementation significantly decreased the level of triglycerides, and although the level of HDL-C increased above the level of non-diabetic controls, the increase was not statistically significant. Serum TG levels are often the first and most striking lipid abnormality seen in diabetes, with significant changes in total cholesterol and LDL-C often occurring later and indicating a more serious dyslipidemia. The early TG responsiveness is due to insulin deficiency- or resistance-induced adipose lipolysis, increased hepatic VLDL production, and decreased clearance of TG-rich lipoproteins by lipoprotein lipase (31). However, these results further support the idea that folate may be involved in the regulation of lipid metabolism. Our findings are consistent with the results of Mutavdzin et al. (2019), who observed similar effects in a streptozotocin-induced diabetic rat model, emphasizing the antioxidant effects of folate (17). However, human studies have been inconsistent, possibly due to dosage, duration, and baseline metabolic conditions (32), as stated by Asbaghi et al. (2021). Mechanistically, HHcy leads to impairment of phospholipid metabolism, especially the balance between phosphatidylcholine (PC) and phosphatidylethanolamine (PE), resulting in triglyceride accumulation. Furthermore, HHcy activates sterol regulatory element-binding proteins (SREBPs), which results in an increase of intracellular triglyceride synthesis, endoplasmic reticulum stress, impairment of lipoprotein processing, and lipid dysregulation (29, 33).

Histopathological studies have shown that STZ-induced diabetes causes severe renal damage, including tubular necrosis, interstitial haemorrhage, inflammatory cell infiltration, and proteinuria (34, 35). The main causes of these structural changes are oxidative stress and inflammation caused by chronic hyperglycaemia (12, 36, 37). The present study demonstrated that folate supplementation mildly reduced inflammatory infiltration and proteinuria in diabetic rats, suggesting a possible role in ameliorating oxidative stress and modulating inflammatory pathways to preserve renal integrity (38, 39). These observations are in line with previous studies indicating that folate ameliorates tubular injury and suppresses inflammation, with a modest overall protective effect (24). However, clinical trials in humans, such as Schneider et al. (2014), have yielded mixed results, possibly due to species-specific differences, different treatment protocols, or the complex pathogenesis of diabetic kidney disease in humans (22). High doses of folate have been linked to nephrotoxic effects, highlighting the need for dose optimization and consideration of clinical context in its therapeutic use (40).

It is important to note that several preclinical studies investigating the renoprotective effects of folate in streptozotocin-induced diabetic models were not designed to include a standard therapeutic comparator but rather to elucidate the independent antioxidant and anti-inflammatory properties of folate. For example, Ebaid et al. and Mutavdzin et al. examined the role of folate supplementation in diabetic rats without insulin or renin-angiotensin system inhibitors and observed a significant decrease in oxidative stress and histopathological damage (17, 24). Similarly, Jing and Chen examined the renoprotective effect of folate via modulation of NF-κB signalling, without comparison with standard antidiabetic therapies (23). Together, these and the present findings support the experimental validity of folate as a single intervention in early diabetic kidney injury but also emphasize the need for future studies incorporating standard therapies for direct therapeutic benchmarking.

The study has some limitations that need to be taken into account when interpreting the findings. In the present study, only a single dose of folate was tested, and further studies with different dosing regimens may help to define the optimal therapeutic range more clearly. Furthermore, the absence of a standard therapeutic comparator (e.g., insulin or an angiotensin-converting enzyme inhibitor) prevents

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direct comparison with established therapies. Functional indices based on urine analysis and quantitative measurement of inflammatory cytokines were not performed. Renal function was partially assessed by serum levels of urea and creatinine and histopathological assessment of kidney tissue. Additional studies with detailed renal functional parameters, inflammatory markers, and mechanistic endpoints may further clarify the protective effect.

Conclusion

Diabetes alters metabolic regulation, increases oxidative stress, and causes structural damage to vital organs, especially the kidneys. In our study, STZ-induced diabetes caused significant renal oxidative damage, as evidenced by increased MDA levels indicating enhanced lipid peroxidation. Folate supplementation normalised MDA levels, highlighting its antioxidant potential in renal tissue. Histology showed some improvement, with less inflammation and proteinuria, but biochemical markers (urea and creatinine) were unchanged. These findings suggest that folate may help attenuate oxidative and metabolic disturbances during the early stages of diabetes. Further studies are required to establish its clinical utility and to explore any synergistic benefits with other therapeutic approaches.

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CRediT authorship contribution statement

Conceptualization, Methodology, Validation, Supervision, Project Administration: AV, AK; Formal Analysis, Software: RM, AV; Investigation: RM, AHR, TSP; Resources: AV, AK, RM; Data Curation, Writing–Original Draft Preparation: RM; Writing–Review & Editing: RM, AV, AK, SS, AHR, TSP; Visualization: RM, SS.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI writing assistance was utilized in the production of this manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical considerations

This study was approved by the Ethical Committee of the University of Tehran with the code of IR.UT.VETMED.REC.1403.045.

Data availability statement

The data that support the findings of this study are available on request.

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