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Morphological features of renal glomerular injury in experimental diabetes mellitus and their correction through the inhibition of cellular protein kinases

Abstract

Relevance. Diabetic nephropathy significantly impairs patients' quality of life, leads to loss of working capacity, and is associated with high mortality. Current scientific trends demonstrate a transition from a conventional approach focused solely on normalising blood glucose levels towards developing comprehensive preventive strategies that block pathogenetic mechanisms directly at the molecular level.

Aim. To investigate the impact of the protein kinase inhibitor sorafenib on the histological structure of the kidney in a model of type 2 diabetes mellitus and during treatment.

Materials and methods. An experimental study was conducted on laboratory rats to model diabetes using a hypercaloric, high-fat diet for 150 days, followed by the induction of diabetes mellitus with streptozotocin. The animals were divided into the following experimental groups and subgroups: Group I: normal-calorie diet. Group II: diabetes modelling comprising subgroups IIa (placebo treatment), IIb (sorafenib treatment), IIc (insulin treatment) and IId (combined insulin and sorafenib treatment). Treatment following the induction of diabetes lasted for 30 days. The animals' kidneys were then examined using general histological and morphometric methods. Paraffin sections were stained with haematoxylin and eosin. The areas of the renal corpuscles and glomeruli, as well as the cell density within the glomeruli, were measured.

Results. Animals in the experimental subgroups IIa, IIb and IIc exhibited moderate changes that predominantly affected the glomeruli. This was manifested by an increase in the glomerular area compared to that of intact animals. Animals in subgroup IIa were more frequently characterised by the presence of both obliterated and dilated capillaries. These capillaries were found within the glomerular loops. In animals in subgroups IIb and IIc, enlargement of the glomeruli was accompanied by dilatation of the capillary loops. The histological structure and morphometric parameters of the renal glomeruli in animals in subgroup IId were similar to those observed in group I. The morphological changes identified in subgroups IIa, IIb and IIc are characteristic of the early stages of diabetic nephropathy, indicating compression of the capillaries due to mesangial expansion and excessive dilatation of other capillaries as a result of hyperfiltration.

Conclusions. Using the protein kinase inhibitor sorafenib alongside the standard insulin therapy regimen prevented the development of the renal glomerular lesions characteristic of diabetic nephropathy.

Keywords: diabetic nephropathy; protein kinase inhibitors; sorafenib; glomerular mesangium; signalling pathways.

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INTRODUCTION

Diabetic nephropathy is one of the most severe and clinically significant complications of diabetes mellitus. It is a leading cause of disability, a substantial reduction in quality of life and high mortality among patients worldwide. For many years, the conventional approach to preventing this condition focused exclusively on achieving intensive glycaemic control. However, evidence has shown that this approach is insufficient to prevent renal failure and kidney fibrosis. Consequently, the modern understanding of the condition's pathophysiology has shifted considerably, moving away from a glucose-centred model and towards identifying and developing strategies that target the molecular and cellular cascades involved in renal injury. Chronic hyperglycaemia triggers a complex cascade of intracellular signalling pathways, in which excessive protein kinase activation plays a pivotal role by inducing oxidative stress, endothelial dysfunction and extracellular matrix expansion. Therefore, investigating the morphological features of renal glomerular injury under conditions of experimentally modelled type 2 diabetes mellitus, together with searching for pharmacological methods of correcting these changes using cellular protein kinase inhibitors, is an important objective of modern fundamental medicine. Such research could lead to new possibilities for developing combined therapeutic regimens aimed at protecting the kidneys.

A review of recent scientific literature reveals a significant interest among researchers in the molecular mechanisms that cause renal tissue damage in diabetes mellitus. H. Xu *et al*. [1] provided a detailed characterisation of the ERK1/2 signalling pathway's role in diabetes mellitus, emphasising its significance in the development of the disease and its potential as a therapeutic target for reducing cellular stress. Investigating the same cascade, Y. Hu *et al*. [2] concluded that activation of the RAF/MEK/ERK signalling pathway in the tubular epithelium directly stimulates epithelial-mesenchymal transition, thereby promoting fibrosis of the renal parenchyma. In an experimental study, C. Lavoz *et al*. [3] demonstrated that blocking VEGFR2 receptors significantly reduces the severity of renal damage in diabetic nephropathy by inhibiting pathological angiogenesis and normalising the permeability of the glomerular barrier. L. Feng *et al*. [4] emphasised the importance of the condition of the mesangium, demonstrating that mesangial cell proliferation and excessive matrix synthesis induced by protein kinases constitute the morphological basis of early glomerular changes. At the systemic level, S. Hu *et al*. [5] identified various therapeutic targets, noting that molecularly targeting intracellular kinases is the most promising strategy for overcoming resistance to standard therapy.

Sorafenib, a multikinase inhibitor that suppresses key components of the RAF/MEK/ERK, VEGFR and PDGFR pathways, is of particular interest in terms of its potential impact on the mechanisms underlying diabetic complications. K. Usenko *et al*. [6] found that the combination of sorafenib and insulin, when used to block protein kinases, effectively prevented the pathological expression of the growth factors VEGF and HIF-1α. This, in turn, reduced the severity of neurodegeneration in retinopathy. In another study, K. Usenko *et al*. [7] demonstrated that sorafenib substantially reduced glial activation and suppressed proliferative processes caused by prolonged metabolic stress. Furthermore, Y. Chen *et al*. [8] confirmed the high biological efficacy of novel sorafenib nanoparticle formulations in preserving tissue histology under conditions of experimental diabetes.

Parallel studies have confirmed the potential of other kinase inhibitors for renal protection. For example, J. Wang *et al*. [9] showed that, in a rat model of diabetes, administration of a selective protein kinase C α and β inhibitor could halt the progressive decline in renal function and substantially reduce the severity of morphological changes in the glomeruli. Meanwhile, X. Zhu *et al*. [10] found that combining the multikinase inhibitor dasatinib with quercetin protected the kidneys against diabetic injury by activating autophagy and restoring podocyte structure. This was directly correlated with improvements in the organ's overall histological parameters. K. Matoba [11] found that inhibiting Rho-associated protein kinase (ROCK) stabilised the glomerular capillary architecture at the tissue level.

The objective of this study was to determine the nature and extent of morphological changes in the renal glomeruli of rats during long-term modelling of type 2 diabetes mellitus, and to evaluate the effectiveness of their therapeutic correction through the administration of the multikinase inhibitor sorafenib, either alone or in combination with insulin.

MATERIALS AND METHODS

The experimental study was conducted on three-month-old male Wistar rats, which were kept in an experimental animal facility under standard conditions: an air temperature of 20-24°C, a relative humidity of 45-65%, natural daylight, and unrestricted access to water and food. All experimental procedures, animal identification, housing, and care were carried out in accordance with Directive 2010/63/EU [12], as well as the provisions of the Ukrainian Law No. 3447-IV [13]. The study protocol was reviewed and approved by the Commission on Bioethical Expertise and Research Ethics of Bogomolets National Medical University (Approval No. 204, 23 March 2026). The sample size was calculated using G*Power software (version 3.1.9.7, Heinrich Heine University Düsseldorf) with the "ANOVA: Fixed effects, omnibus, one-way" statistical test to compare mean values among five groups. A significance level of $\alpha = 0.05$ and a statistical power of 80% were adopted for the power analysis.

The experimental animals were allocated to groups using simple randomisation. Before the start of the

study, identification numbers were assigned to all rats by marking their tails. The animals were randomised into the following groups using a random number generator – the RANDBETWEEN function in Microsoft Excel: Group I (n = 9; normal-calorie diet): the animals received standard pelleted feed (PK 120-1, Rezon Private Enterprise, Ukraine) before and after reaching three months of age. This feed contained 3,295 kcal/kg, 23% crude protein, 6.6% fibre, and 6% fat. Group II (n = 36, high-calorie diet and induction of insulin resistance): after reaching three months of age, the animals received a high-calorie diet enriched with fat and fructose for 150 days. This diet contained 5,260 kcal/kg and had a fat content of 56.7%. At the end of this period, the animals received a single intraperitoneal injection of streptozotocin at a dose of 25 mg/kg. They then continued to receive the high-calorie diet for a further 30 days and were divided into the following subgroups: Subgroup IIa (n = 9, placebo treatment): the animals received 5 ml of physiological saline orally once daily; Subgroup IIb (n = 9, sorafenib treatment): the animals received an oral suspension of sorafenib in 5 ml of physiological saline at a dose of 50 mg/kg (Soranib, Cipla, India); Subgroup IIc (n = 9, insulin treatment): the animals received ultra-short-acting insulin intraperitoneally at a dose of 30 IU/kg (Actrapid HM, Novo Nordisk, Denmark) every other day; Subgroup IId (n = 9, combined sorafenib and insulin treatment): the animals received insulin and sorafenib according to the protocols used for subgroups IIb and IIc.

On day 180, all the animals were euthanised with an overdose of thiopental, which was administered intraperitoneally at a dose of 75 mg/kg. Kidney fragments were collected for light microscopic examination and fixed by immersion in 10% buffered formalin (PBS, pH 7.2; Sigma-Aldrich, USA) for 72 hours. The samples were then dehydrated in a graded series of isopropyl alcohol solutions and embedded in Paraplast Plus (McCormick, USA). Sections were prepared using an Accu-Cut Sakura SRM-200 microtome (Sakura, USA). The resulting sections were stained with haematoxylin and eosin. The stained histological specimens were photographed using a MicroMed Evolution ES-4130 microscope (MicroMed, People's Republic of China) and analysed using version 1.50 of the ImageJ biomedical image analysis software (National Institutes of Health, USA). For the morphometric analysis, the areas of the renal corpuscles and glomeruli, as well as the cell density within the glomeruli, were calculated in randomly selected microscopic fields. The distribution of the numerical data was tested for normality using the D'Agostino-Pearson test. Intergroup comparisons were performed using the Kruskal-Wallis test in Prism statistical software (version 11.0.0, GraphPad, USA). Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Light microscopic examination of haematoxylin- and eosin-stained sections from Group I animals on a normal-calorie diet revealed that the histoarchitecture of the organ, consisting of parenchyma and stroma, was intact. The renal parenchyma consisted of renal corpuscles and tubules belonging to different segments of the nephron (Fig. 1A). The renal corpuscles consisted of capillary glomeruli and capsules. A wide, clearly visible urinary space was present. The capsule looked like a thin, rounded structure made up of flattened epithelial cells. In transverse sections, the capillary lumina were clearly visible and round or triangular in shape. Tubules of different diameters were observed. The tubular epithelial cells had uniformly stained eosinophilic cytoplasm. The nuclei were centrally located. In some tubules, the epithelial cells exhibited a surface brush border corresponding to the microvilli of proximal tubular epithelial cells.

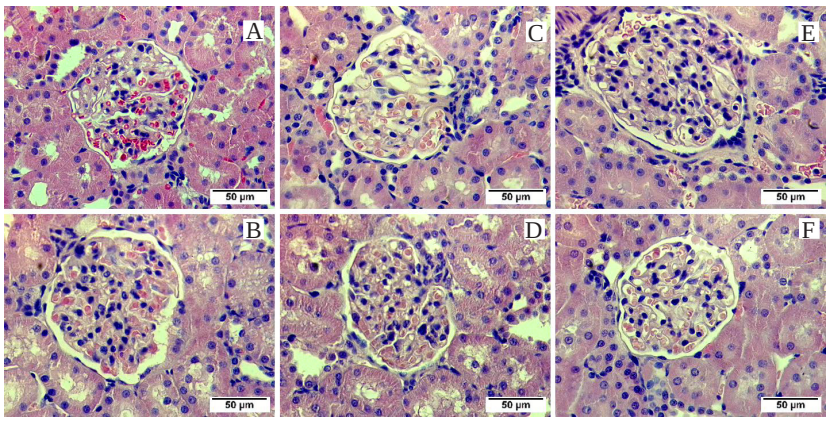

Figure 1. Histological structure of the renal corpuscles in rats from the different group

Note: A – Group I; B and C – Subgroup IIa (diabetes induction and placebo treatment); D – Subgroup IIb (diabetes induction and sorafenib treatment); E – Subgroup IIc (diabetes induction and insulin treatment); F – Subgroup IId (diabetes induction and insulin and sorafenib treatment). Haematoxylin and eosin stainin

Source: compiled by the authors

In subgroup IIa animals, which were fed a high-calorie diet, made diabetic and given a placebo, the histoarchitecture of the organ was preserved and similar to that observed in the previous group. The renal parenchyma contained renal corpuscles and tubules of various diameters. The renal corpuscles consisted of a capsule and a capillary glomerulus. The glomeruli were visibly enlarged. Unlike Group I animals, most of the glomeruli in this subgroup contained capillaries without a clearly visible lumen (Fig. 1B), or exhibited dilated capillaries with increased diameters within the glomerular loops (Fig. 1C). The mesangium appeared as a homogeneous mass containing a moderate number of cells. The tubules contained eosinophilically stained desquamated epithelial cells.

In subgroup IIb animals, which received a high-calorie diet, underwent diabetes induction, and were treated with sorafenib, the renal structure was preserved. The parenchyma was made up of renal corpuscles and tubules that corresponded to different parts of the nephron. In more than half of the renal corpuscles, the urinary space was clearly visible around the periphery of the glomerulus. Most glomeruli were enlarged with a narrowed urinary space and consisted of capillaries with narrowed lumina. More than half of the capillaries had no clearly visible lumen (Fig. 1D). The mesangium contained a moderate number of cells, which were unevenly distributed within the glomerulus and which were present in areas without cells. The tubules contained eosinophilically stained desquamated epithelial cells. In animals in subgroup IIc that received a high-calorie diet, underwent diabetes induction, and were treated with insulin, the renal structure was similar to that observed in the previous subgroup, characterised by enlarged glomeruli. However, a greater number of glomerular capillaries exhibited visible round or linear lumina depending on their orientation relative to the sectioning plane. Some glomeruli contained loops with dilated capillaries (Fig. 1E). The glomeruli exhibited a clearly visible urinary space and a capsule composed of flattened epithelial cells. The mesangium contained a homogeneous, pale pink matrix and a moderate number of evenly distributed cells. In animals in subgroup IId that received a high-calorie diet, underwent diabetes induction, and were treated with insulin and sorafenib, the renal structure was preserved. The renal corpuscles were normal in size, and the glomeruli were clearly separated from the capsule by the urinary space. The glomeruli had a clearly visible urinary space and a capsule composed of flattened epithelial cells (Fig. 1F). The mesangium contained a homogeneous, pale pink matrix and a moderate number of evenly distributed cells.

Morphometric analysis revealed significant differences in renal corpuscle area among animals from the various study groups and subgroups ($p < 0.001$) (Table 1). Intergroup comparisons revealed that this parameter was significantly higher in rats from subgroups IIa, IIb, and IIc than in Group I animals. The renal corpuscle area in subgroup IId, which received combined treatment, did not differ significantly from that in group I animals. The glomerular area followed a similar pattern to the renal corpuscle area across the groups. Intergroup comparisons revealed that the glomerular area was significantly larger in rats from subgroups IIa, IIb, and IIc than in Group I animals. The glomerular area in subgroup IId, which received combined treatment, did not differ significantly from that in group I.

Table 1. Morphometric parameters of renal corpuscles in animals from the different experimental groups

Animal group/ subgroup	Renal corpuscle area, μm², median (25th-75th percentile)	Glomerular area, μm², median (25th-75th percentile)	Cell density, cells per 1,000 μm²
I	7,856 (6,216-8,750)	6,636 (5,327-7,738)	7.1 (6.4-7.9)
IIa (placebo)	9,487 (8,333-10,716)*	8,011 (7,343-8,903)*	6.8 (6.4-7.5)
IIb (sorafenib)	9,741 (8,617-11,770)*	7,724 (6,694-9,280)*	6.6 (6.2-7.4)
IIc (insulin)	9,572 (7,927-11,218)*	7,953 (6,575-9,218)*	7.4 (7.0-8.0)
IId (insulin + sorafenib)	7,235 (6,604-8,123)	6,137 (5,571-7,062)	7.4 (6.6-8.0)

Note: * – $p < 0.05$ compared with Group I animals
Source: compiled by the authors

There was no significant difference in cell density among animals from the different groups and subgroups ($p > 0.05$ for all pairwise comparisons). Under conditions of experimentally induced diabetes mellitus in rats, a statistically significant increase in renal corpuscle and glomerular areas was observed in subgroups IIa (placebo), IIb (sorafenib), and IIc (insulin), compared to Group I animals ($p < 0.05$). The most pronounced changes, including both obliterated and dilated capillary loops, were observed in the placebo group. Sorafenib or insulin monotherapy partially modified the nature of the glomerular changes, but neither prevented glomerular hypertrophy. Only the combined administration of insulin and sorafenib in subgroup IId maintained morphometric parameters of renal corpuscles and glomeruli, which did not differ statistically from those in Group I. This treatment was also associated with an even distribution of cells within the mesangium and preservation of the normal architecture of the glomerular capillaries.

The morphological changes identified in Group II predominantly affected the glomeruli and involved the tubular portion of the nephrons to a lesser extent. The glomerular changes can be regarded as moderate in severity. They may represent the initial manifestations of diabetic nephropathy, which can be explained by the relatively short duration of the experiment. These changes correspond to the early stages of the disease: according to the current Renal Pathology Society classification, Class I is characterised by thickening of the glomerular basement membrane, and Class IIa/IIb is characterised by mild or moderate mesangial expansion. This classification remains the principal instrument for histopathological assessment of diabetic nephropathy, as described by H. Qasim *et al*. [14]. In their review, H. Thomas & A. Ford Versypt [15] analysed the pathophysiology of mesangial expansion in detail. They emphasised the roles of biomechanical stress, signalling pathways such as TGF-β and MAPK, and extracellular matrix accumulation as key mechanisms underlying the early changes that occur in the glomeruli of patients with diabetic nephropathy. Consistent with these findings, animals in subgroups IIa, IIb, and IIc of the experimental group exhibited enlargement of the renal corpuscles due to glomerular hypertrophy, while the urinary space remained relatively intact. Along with the presence of dilated capillary loops, this may be functionally equivalent to hyperfiltration, which is characteristic of the initial manifestations of diabetic nephropathy. This phenomenon is associated with the development of hyperglycaemia and the subsequent increase in glucose and sodium reabsorption in the proximal tubule. This reduces the delivery of sodium and chloride ions to macula densa cells. This suppresses tubuloglomerular feedback, reduces adenosine production, and causes relative dilatation of the afferent arteriole. Ultimately, this increases glomerular hyperfiltration. Y. Yang & G. Xu [16] reported that this process leads to glomerulomegaly and mechanical stress on mesangial cells and podocytes over time, thereby contributing to disease progression.

Narrowing and obliteration of the glomerular capillary lumina were also identified, with the most pronounced signs observed in subgroups IIa and IIb. These changes were likely caused by mesangial expansion. In their review of the risk factors, progression and mechanisms of diabetic nephropathy, V. Natesan & S. Kim [17] emphasised that hyperglycaemia induces the activation of protein kinases, oxidative stress, and the excessive accumulation of extracellular matrix components, including fibronectin, laminin and collagen, within the mesangium. This leads to mesangial expansion and the subsequent mechanical compression of the glomerular capillary loops. In the absence of statistically significant changes in glomerular cell density, the expansion of the mesangial space in subgroups IIa and IIb was likely predominantly caused by the accumulation of non-cellular matrix. However, definitive confirmation of this mechanism requires additional immunohistochemical and electron microscopic investigations.

The effectiveness of insulin therapy in subgroup IIc was demonstrated through the partial preservation of visible capillary lumina. This can be attributed to a reduction in the direct cytotoxic effects of hyperglycaemia on endothelial and mesangial cells. Nevertheless, glycaemic control alone was ineffective in preventing an increase in glomerular area, thus confirming the limitations of this glucose-centred approach. Even after blood glucose normalisation, previously activated intracellular signalling cascades may continue to stimulate matrix synthesis and cellular hypertrophy. D. Viggiano [18] showed that strict blood sugar control can slow down but not stop the progression of diabetic nephropathy because a significant part of the harmful processes, such as inflammation, fibrosis, endothelial dysfunction and matrix accumulation, continue to be active even when blood sugar levels are normalised. Sorafenib, a multikinase inhibitor, would theoretically be expected to block proliferative signals by inhibiting VEGF and PDGF receptors, which play key roles in mesangial expansion, when administered to subgroup IIb. However, when administered as monotherapy without correcting hyperglycaemia, it did not produce a statistically significant improvement in morphometric parameters compared with a placebo. This may indicate that the metabolic stress in the present model was so intense that inhibiting individual kinases without controlling the metabolism was ineffective.

The most pronounced protective effect was demonstrated by the combined treatment of subgroup IId. This may be due to synergism: insulin reduced the direct metabolic impact of hyperglycaemia, while sorafenib blocked residual pathological activation of protein kinases and growth factors. This enabled glomerular morphometric parameters to be maintained at physiological levels. These results are consistent with current strategies for modulating protein kinase signalling pathways. D. Dorotea *et al*. [19] demonstrated that inhibiting pan-Src kinases, particularly Fyn, reduces endoplasmic reticulum stress, inflammation, and fibrosis in models of diabetic kidney injury. In their review of Rho/ROCK signalling in renal diseases, W. Xiong *et al*. [20] demonstrated that inhibiting this pathway reduces proteinuria, mesangial expansion, and fibrosis in models of diabetic nephropathy. S. Al-Masri *et al*. [21] emphasised the potential value of targeting PKC and other kinase pathways in combination with standard treatment. Furthermore, S. Sinha & S. Nicholas [22] confirmed the role of PKC in the development of diabetic microvascular complications, including mesangial expansion.

The scientific novelty of the findings lies in demonstrating for the first time in an experimental model of diabetes mellitus that the multikinase inhibitor

sorafenib may protect the renal glomeruli when administered alongside insulin therapy. These results suggest that developing adjunctive therapeutic regimens for patients with diabetic nephropathy, based on the targeted modulation of molecular mechanisms alongside standard glucose-lowering therapy, could be valuable. They also demonstrate the need for further experimental and clinical studies.

CONCLUSIONS

1. In an experimental model of type 2 diabetes mellitus in rats, statistically significant increases in renal corpuscle and glomerular areas were observed in subgroups IIa (placebo), IIb (sorafenib) and IIc (insulin), compared with intact group I animals ($p < 0.05$). The median renal corpuscle area ranged from 9,487 to 9,741 μm^2, while the median glomerular area ranged from 7,724 to 8,011 μm^2. This is in contrast to the control group, where the respective median values were 7,856 μm^2 and 6,636 μm^2. Morphological examination of subgroups IIa, IIb and IIc revealed changes characteristic of the early stages of diabetic nephropathy. These changes included glomerular hypertrophy and irregularity of the capillary loop lumina, with both obliterated and dilated capillaries present, as well as moderate expansion of the mesangial matrix. These changes indicate the presence of hyperfiltration and mesangial expansion.

2. Administering sorafenib alone in subgroup IIb or insulin alone in subgroup IIc did not prevent glomerular hypertrophy and only produced minor correction of the structural remodelling of the glomeruli.

3. The most pronounced morphoprotective effect was demonstrated by the combined administration of insulin and sorafenib in subgroup IId. The renal corpuscle area was 7,235 μm^2, with a 25th-75th percentile range of 6,604-8,123 μm^2, while the glomerular area was 6,137 μm^2, with a 25th-75th percentile range of 5,571-7,062 μm^2. These values did not differ statistically from those of intact Group I animals ($p > 0.05$). The histological structure of the glomeruli approached normality, with a clearly defined urinary space, even cell distribution within the mesangium, and normal capillary loop architecture.

4. There was no significant difference in glomerular cell density among the groups ($p > 0.05$), which may indicate that accumulation of the extracellular matrix predominates in the mechanism of mesangial expansion during the early stages of diabetic nephropathy.

5. It is important to note that this study has certain methodological limitations. In particular, the findings were based solely on light microscopic morphometric data. A comprehensive understanding of sorafenib's mechanisms of action requires further histochemical, electron microscopic, and immunohistochemical investigations. Future studies should evaluate the effect of cellular protein kinase inhibition on the proportional areas occupied by the mesangial matrix and collagen within the glomeruli, as well as on the expression of inflammatory and angiogenic markers in rat kidneys, employing immunohistochemical methods.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

[1] Xu H, Liu T, Dai Y, Li N, Cao Z. The role of ERK1/2 signaling in diabetes: Pathogenic and therapeutic implications. Front Pharmacol. 2025;16:1600251. DOI: 10.3389/fphar.2025.1600251

[2] Hu Y, Tang W, Liu W, Hu Z, Pan C. Astragaloside IV alleviates renal tubular epithelial-mesenchymal transition via the CX3CL1-RAF/MEK/ERK signaling pathway in diabetic kidney disease. Drug Des Devel Ther. 2022;16:1605–20. DOI: 10.2147/DDDT.S360346

[3] Lavoz C, Rodrigues-Diez RR, Plaza A, Carpio D, Egido J, Ruiz-Ortega M, et al. VEGFR2 blockade improves renal damage in an experimental model of type 2 diabetic nephropathy. J Clin Med. 2020;9(2):302. DOI: 10.3390/jcm9020302

[4] Feng L, Feng YY, Ren Q, Fu P, Ma L. Mesangial cells in diabetic kidney disease: From mechanisms to therapeutic implications. Int J Biol Sci. 2025;21(11):4762–81. DOI: 10.7150/ijbs.114907

[5] Hu S, Lee K, He JC, Fan Y. Current landscape and emerging therapeutic targets in diabetic kidney disease. Clin J Am Soc Nephrol. 2026. DOI: 10.2215/CJN.0000001053

[6] Usenko KO, Strubchevska O, Rykov SO, Babenko MS, Strubchevska K, Kozyk O, et al. Growth factor and hypoxia-inducible factor alpha content in the retina of male Wistar rats in experimental diabetic retinopathy and the effect of cellular protein kinase blockade. Front Endocrinol. 2025;16:1643445. DOI: 10.3389/fendo.2025.1643445

[7] Usenko KO, Ziablitsev SV, Yevstifeiev DI, Dyadyk OO, Popova KI. Retinal glial activation in diabetic retinopathy: Therapeutic impact of multikinase inhibition with sorafenib. Wiad Lek. 2025;7:1309–18. DOI: 10.36740/WLek/208991
[8] Chen Y, Liu B, Zhang X, Xie R, Li J, Qu J, et al. Sorafenib nanoparticles coated with Eudragit RL for ocular drug delivery: A potential treatment for diabetic retinopathy. Int J Pharm X. 2026;11:100523. DOI: 10.1016/j.ijpx.2026.100523
[9] Wang J, Casimiro-Garcia A, Johnson BG, Duffen J, Cain M, Savary L, et al. A protein kinase C α and β inhibitor blunts hyperphagia to halt renal function decline and reduces adiposity in a rat model of obesity-driven type 2 diabetes. Sci Rep. 2023;13:16919. DOI: 10.1038/s41598-023-43759-7
[10] Zhu X, Zhang C, Liu L, Xu L, Yao L. Senolytic combination of dasatinib and quercetin protects against diabetic kidney disease by activating autophagy to alleviate podocyte dedifferentiation via the Notch pathway. Int J Mol Med. 2024;53(3):26. DOI: 10.3892/ijmm.2024.5350
[11] Matoba K. Harnessing ROCK biology to revolutionize diabetic nephropathy: Decoding mechanisms, designing therapies. Diabetol Int. 2026;17:3. DOI: 10.1007/s13340-025-00861-7
[12] Directive 2010/63/EU of the European Parliament and of the Council. On the Protection of Animals Used for Scientific Purposes [Internet]. 2010 October 20 [cited 2026 January 8]. Available from: https://eur-lex.europa.eu/eli/dir/2010/63/oj
[13] Law of Ukraine No. 3447-IV. On the Protection of Animals from Cruelty [Internet]. 2006 February 21 [cited 2026 January 8]. Available from: https://zakon.rada.gov.ua/laws/show/3447-15
[14] Qasim H, Dibian S, Hayajneh A, Khattab K, Leoni MLG, Varrassi G. Histopathology of diabetic nephropathy: Beyond glomerular basement membrane thickening. Cureus. 2025;17(9):e93497. DOI: 10.7759/cureus.93497
[15] Thomas HY, Ford Versypt AN. Pathophysiology of mesangial expansion in diabetic nephropathy: Mesangial structure, glomerular biomechanics, and biochemical signaling and regulation. J Biol Eng. 2022;16:19. DOI: 10.1186/s13036-022-00299-4
[16] Yang Y, Xu G. Update on pathogenesis of glomerular hyperfiltration in early diabetic kidney disease. Front Endocrinol. 2022;13:872918. DOI: 10.3389/fendo.2022.872918
[17] Natesan V, Kim SJ. Diabetic nephropathy – a review of risk factors, progression, mechanism, and dietary management. Biomol Ther. 2021;29(4):365–72. DOI: 10.4062/biomolther.2020.204
[18] Viggiano D. Mechanisms of diabetic nephropathy not mediated by hyperglycemia. J Clin Med. 2023;12(21):6848. DOI: 10.3390/jcm12216848
[19] Dorotea D, Jiang S, Pak ES, Son JB, Choi HG, Ahn SM, et al. Pan-Src kinase inhibitor treatment attenuates diabetic kidney injury via inhibition of Fyn kinase-mediated endoplasmic reticulum stress. Exp Mol Med. 2022;54:1086–97. DOI: 10.1038/s12276-022-00810-3
[20] Xiong W, Miao D, Hou Z, Zhang X, Xiong Z. Rho/ROCK signaling pathway in kidney diseases: Mechanisms and therapeutic perspectives. Biomedicines. 2026;14(3):621. DOI: 10.3390/biomedicines14030621
[21] Al-Masri S, Coelho JN, Thomas L. Molecular pathways and emerging therapeutic targets in the pathogenesis of diabetic kidney disease. Front Physiol. 2026;17:1747053. DOI: 10.3389/fphys.2026.1747053
[22] Sinha SK, Nicholas SB. Pathomechanisms of diabetic kidney disease. J Clin Med. 2023;12(23):7349. DOI: 10.3390/jcm12237349

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Морфологічні особливості ураження клубочків нирок при експериментальному цукровому діабеті та їх корекція шляхом гальмування клітинних протеїнкіназ

Анотація

Актуальність. Діабетична нефропатія належить до критичних ускладнень, що суттєво погіршує якість життя пацієнтів, призводить до втрати працездатності та високої летальності. Сучасні наукові тренди демонструють перехід від класичного підходу, зосередженого виключно на нормалізації рівня глюкози, до розробки комплексних стратегій профілактики, які базуються на блокуванні патогенетичних механізмів безпосередньо на молекулярному рівні.

Мета. Визначити вплив інгібітора протеїнкіназ (сорафенібу) на гістологічну структуру нирки при експериментальному моделюванні цукрового діабету другого типу та його лікуванні.

Матеріали та методи. Проведено експериментальне дослідження на лабораторних тваринах (щурах) із моделюванням діабету шляхом використання гіперкалорійної, високожирової дієти протягом 150 діб та подальшої індукції цукрового діабету стрептозотоцином. Тварини були розділені на такі дослідні групи та підгрупи: I група – нормокалорійна дієта; II група – моделювання діабету, підгрупа IIa (лікування плацебо); IIb (лікування сорафенібом), IIc (лікування інсуліном), IId (лікування інсуліном і сорафенібом). Тривалість лікування після індукції діабету становила 30 діб. Нирки тварин забирали для загальногістологічного і морфометричного дослідження. Парафінові зрізи забарвлювали гематоксиліном-еозином, підраховували площу ниркових тілець, площу клубочків, питому кількість клітин у складі клубочка.

Результати. У тварин експериментальних підгруп IIa, IIb, IIc відзначалися помірні зміни переважно у клубочках у вигляді збільшення їх площі, у порівнянні із інтактними тваринами. Для тварин IIa групи більше була характерна наявність як облітерованих, так і розширених капілярів у складі петель клубочків. Для тварин підгруп IIb та IIc поруч із збільшенням у розмірах, відзначалося розширених капілярних петель. Гістологічна структура та морфометричні параметри клубочків нирок у тварин підгрупи IId наближалися до таких у тварин I групи. Виявлені у тварин підгруп IIa, IIb, IIc морфологічні зміни були характерними для початкових стадій діабетичної нефропатії і свідчили як про здавлення капілярів за рахунок розширення мезангіуму, так і перерозширення інших капілярів внаслідок гіперфільтрації.

Висновки. Застосування інгібітора протеїнкіназ сорафенібу як доповнення до стандартної схеми інсулінотерапії попереджало появу характерних для діабетичної нефропатії ознак ураження ниркових клубочків.

Ключові слова: діабетична нефропатія; інгібітори протеїнкіназ; сорафеніб; мезангіум клубочка; сигнальні шляхи.