



# Diabetic Nephropathy as an Experimental Way to Model Chronic Renal Failure

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## ABSTRACT

**Background:** As is known, the modeling of chronic renal failure against the background of diabetic nephropathy is associated with the need to maximally approximate the conditions for its reproduction to the clinical one. Based on the foregoing, the priority in the reproduction of chronic renal failure should come from the modeling of diabetes mellitus, in particular diabetic nephropathy.

**Purpose:** To develop an experimental model of chronic renal failure against the background of diabetic nephropathy.

**Methods:** Experimental studies were carried out on rabbits with the choice of the optimal method from 5 series of experiments. The evaluation was carried out according to the abortive course of the process, the development of hyperglycemic coma, the presence of angiodilation and the reproducibility of the model. For morphological studies, tissue samples in the form of pieces of kidney tissue were taken by performing an operation under ether anesthesia.

**Results:** The 3 stages of nephropathy identified by us during the experiment (I-minor, II-moderate and III-severe) testified to the choice of terms for modeling chronic renal failure. The main criteria for a possible period of transition from nephropathy to the development of chronic renal failure is the presence of hyalinosis of microvessels with thickening of the membranes, which indicated the occurrence of irreversible angiogenic changes. This period is defined by us as 40 days of modeling diabetic nephropathy.

**Conclusion:** In the development of chronic renal failure in a model with diabetic nephropathy, both the lack of expression of the angiogenic factor VEGF by podocytes and tubular epithelial cells and the increased expression of the antiangiogenic factor thrombospondin-1 in the renal glomeruli and interstitium play a certain role in the disruption of angiogenesis. Thrombospondin-1 inhibits the proliferation of endothelial cells stimulated by VEGF and oFRF, causing their apoptosis. As a result, the density of glomerular and peritubular capillaries decreases, glomerulosclerosis and interstitial fibrosis develop.

**Keywords:** Diabetes mellitus; Diabetic nephropathy; Experimental modeling; Hyperglycemic

## INTRODUCTION

The reproduction of chronic renal failure against the background of diabetic nephropathy, today, is becoming increasingly important [1,2]. This is due, on the one hand, to the high proportion of the prevalence of this form of diabetes mellitus complication in clinical practice, and, on the other hand, to the need to develop adequate methods of drug correction of this pathology in experimental

conditions [3,4].

As is known, the modeling of chronic renal failure against the background of diabetic nephropathy is associated with the need to maximally approximate the conditions for its reproduction to the clinical one [5-8] Based on the foregoing, the priority in the reproduction of chronic renal failure should come from the modeling of diabetes mellitus, in particular diabetic nephropathy

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[9,10].

The objective of the developed method was to create a method that would improve the accuracy of the reproduction of the model of diabetic nephropathy.

## MATERIALS AND METHODS

The first version of the model of diabetes mellitus was a model in which, under aseptic conditions under ether anesthesia, the animals underwent laparotomy, followed by resection of a flat half of the pancreas from the caudal pole (Series 1). When animals had relatively smaller volumes of the pancreas (1/3 of the tail part) removed, diabetes mellitus did not occur in 75% of cases—the animals recovered. There were no signs of hyperglycemia in the blood, and bio microscopy of the vascular bed of the tissues of the extremities, carried out 7-10 days after modeling, revealed intravascular erythrocyte aggregation in 40% of cases, and the absence of any vasomotor disorders in 45% of cases. Only in those 10-15% in which the disease occurs, a decrease in the arteriolo-venular ratio to 1:2 and extravascular inflammatory reactions in the form of edema were found. When removing large volumes (up to 2/3 of the free part of the pancreas), in 90% of cases, rabbits died from hyperglycemic coma with a high level of glycemia in the blood in the next 3-4 days (series 2). Bio microscopy revealed intravascular stasis with hemorrhage into tissue structures in these rabbits. In a word, even though diabetes mellitus was formally reproduced, in essence, we were dealing with a hyperglycemic coma, the initial onset of which was the removal of the main part of the pancreas, including its secretory zone.

To clarify this issue, we conducted other series of experiments in which the chemical method of modeling diabetes mellitus was used, that is, by reproducing the model because of the introduction of certain organic substances that damage the  $\beta$ -cells of the pancreatic islets. The value of chemical models lies in the fact that they can be reproduced in representatives of a wide variety of species, in small animals, as well as in animals with diffuse pancreas. Chemical shutdown of the islet apparatus is not accompanied by a violation of the exocrine function of the pancreas. The chemical models are also noteworthy because some of the substances that cause diabetes are metabolic products in humans and animals (series 3 and 4).

The results of these series of experiments were generally like those described above, namely: when using alloxan at a dose of 200-300 mg/kg of body weight, in 85.7% of cases, the animals developed a pattern of hyperglycemic coma (Series 3) with a fatal outcome within 10 days after intravenous administration of a chemical agent. This was associated with fulminant damage to insulin-producing pancreatic  $\beta$ -cells, which corresponded to the development of type 1 diabetes mellitus (insulin dependent) and did not meet the requirements for reproducing diabetic nephropathy. In other words, diabetic nephropathy simply did not have time to develop in these terms of diabetes.

To prolong the process of damage to  $\beta$ -cells, as well as to prevent the development of a fulminant course of diabetes mellitus and bring the process closer to clinical conditions, we for the first time used the drug doxorubicin as a chemical substance, which has a side effect of a selective effect on pancreatic  $\beta$ -cells. The drug was administered intraperitoneally at a dose of 100-110 mg/kg in 0.9% sodium chloride solution (series 4). With intraperitoneal administration of doxorubicin, the outcomes were different: out of 21 rabbits, 2 (9.5%) died from hyperglycemic coma, in 14 (66.7%)

the process took an abortive course and only 5 (23.8%) developed a typical picture of diabetes mellitus with stable hyperglycemia.

Comprehension of the stated facts led us to the following three conclusions. First, massive removal or chemical damage to the pancreas, regardless of the nature of the agent, does not lead to the development of diabetic nephropathy in the clinical sense of this term, but to hyperglycemic coma due to the lack of insulin in the body. Secondly, the severity of the condition is so great that diabetic nephropathy, and even more so chronic renal failure, simply does not have time to develop.

This logically led us to the third: chronic renal failure in diabetic nephropathy as a special form of vascular complication of diabetes mellitus is possible only if there is a full-fledged link in the pathogenetic mechanism of its development.

As is known, the mechanism of microangiopathies consists of non-enzymatic glycosylation of capillary basement membrane proteins under conditions of hyperglycemia and activation of the conversion of glucose into sorbitol under the influence of aldose reductase (normally 1-2% of intracellular glucose is converted into sorbitol, and in diabetic angiopathy this figure is 8-10 times higher norms). An excess of sorbitol in the vascular bed leads to thickening and compaction of the vessels themselves. This, in turn, leads to disruption of blood flow in the vessels of the microvasculature with the development of tissue ischemia. There is a vicious circle with glycosylation of basement membrane proteins and accumulation of sorbitol in the walls of micro vessels. As a result of the course of this pathological process, the structure of the cells of the walls of the vessels is disturbed, the structures of the proteins of the intercellular substance of the vascular walls change with the acquisition of antigenic properties by them. All this testifies to the high role of sorbitol in the development of diabetic angiopathy and neuropathy, which means that the use of this substrate in the process of modeling this pathological condition has a natural biological character.

Experimental confirmation of this was obtained in a new series of experiments (series 5), which differed from the previous one in that in order to increase the reproducibility of the model and bring the process closer to the clinical course under ether anesthesia according to our invention, 100-110 mg/kg of doxorubicin preparation in 0.9% sodium chloride solution, and 48 hours after the administration of doxorubicin, 0.2-0.4 ml of 70% sorbitol solution was injected intraperitoneally and retroperitoneally once daily for 3 days.

In dynamics, starting from the first day after the injection of sorbitol, the development of diabetic nephropathy was observed. Over the next 3-4 days, the rabbits developed a clinical picture of diabetes mellitus (hyperglycemia, polyuria, glycosuria), and on the 10-20th day of diabetic nephropathy: a violation of the permeability of the vascular walls, the formation of micro aneurysms, the formation of micro thrombi, the expansion of venules and post capillaries, neoplasms micro vessels, micro hemorrhage, formation of seals and scars in the perivascular tissue of the kidneys.

Conducted intra vital studies of microcirculation in the kidneys of this series of experiments revealed the presence of intravascular disorders in the form of thrombosis, an increase in arteriolo-venular ratios up to 1:4-1:6, with a pronounced infiltration of tissues of extravascular zones. Here we deliberately do not dwell on these issues in more detail since they will be discussed later.

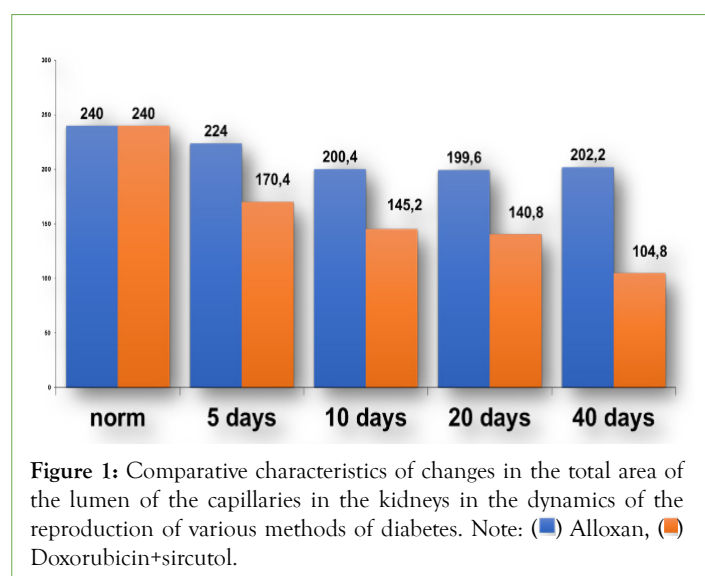
Such consequences (Table 1) of the combined modeling method occurred in 22 (73.3%) of 30 rabbits of this series; in 2 (6.7%) animals, only paralytic expansion of capillaries and an increase in vessel diameters were detected, 2 (6.7%) rabbits died from hyperglycemic coma, and 4 (13.4%) animals did not develop diabetes mellitus.

**Table 1:** Results of different ways to reproduce diabetes mellitus and diabetic nephropathy.

Criterion	Series 1	Series 2	Series 3	Series 4	Series 5
Reverse flow	15 (75%)	-	-	14 (66, 7%)	4 (13, 3%)
Hyperglycemic coma	-	18 (90%)	18 (85, 7%)	2 (9, 5%)	2 (6, 7%)
Expansion of capillaries	5 (25%)	2 (10%)	3 (14,3%)	-	2 (6, 7%)
Reproducibility	-	-	-	5 (23, 8%)	22 (73, 3%)

It is possible that diabetes mellitus in these animals was hidden. However, animals that did not have morphofunctional confirmation of the development of diabetic nephropathy were removed from the subsequent study.

Comparative characteristics of changes in the total area of the lumen of the capillaries in the kidneys in the dynamics of reproduction of various methods of diabetes mellitus showed that the normal state of the area equal to 240 mm<sup>2</sup> progressively decreased with the introduction of sorbitol against the background of doxorubicin utilized by the body. These changes were noted in all series of experiments and were characterized by their reliability both in relation to the control series and in relation to the group of animals with alloxan diabetes (Figure 1). Accordingly, morphometric parameters were also characterized by specific changes within the groups themselves, namely: counting and calculation of the capillary/non-capillary ratio also indicated a decrease in capillary areas compared to nephron areas. Moreover, the capillary/non-capillary ratio of 1:8.4, which took place in the control series of experiments, did not change significantly in alloxan diabetes. However, the introduction of sorbitol led to a progressive decrease in the ratio, which reached the ratio of 1:73.4 by the 40th day of modeling.



The second step in our research work was the selection of the optimal model of chronic renal failure. The currently known methods for modeling chronic renal failure are largely based on the creation of surgical methods. The most widely used technique is subtotal nephrectomy. As a result, acute renal failure develops, turning into chronic, which in clinical practice is equivalent to a shock kidney and its consequences. These variants of models of chronic renal failure also do not correspond to the clinical and morphological characteristics of diabetic nephropathy in the variant where the level of damage falls on arterioles and the capillary network of the kidney. Functional insufficiency of the kidneys as a result of an acute decrease in its volume is more characteristic of the consequences of operations of oncological genesis, the study of which was not included in the goals and objectives of our research.

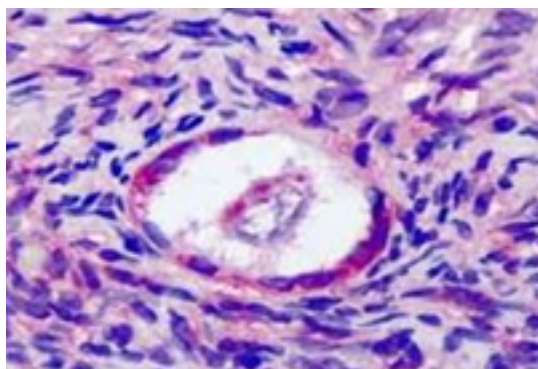
The aim of the experiments was to increase the reproducibility and reliability of chronic renal failure against the background of a model of diabetic nephropathy in laboratory animals by anatomically preserving the organ in the body. Given that the main glomerular apparatus is in the subcortical zone of the kidney, we decided to coagulate the surface of the kidneys while maintaining their anatomical location. To do this, under ether anesthesia, the kidneys were mobilized in animals by translumbar access and diffuse wounds were applied to the cortical layer of the kidneys with an electrocoagulation.

Thus, the above methods of modeling diabetic nephropathy and electrothermal burns of the kidneys have their own distinctive features, isolated by the mechanisms of their reproduction. Reproduction of the model of diabetes mellitus, considering the pathogenetic significance of the role of sorbitol in the development of angiopathy, makes it possible to obtain the possibility of studying nephropathy at a reliable level. At the same time, the preservation of the organ avoids possible errors associated with situations of acute renal failure.

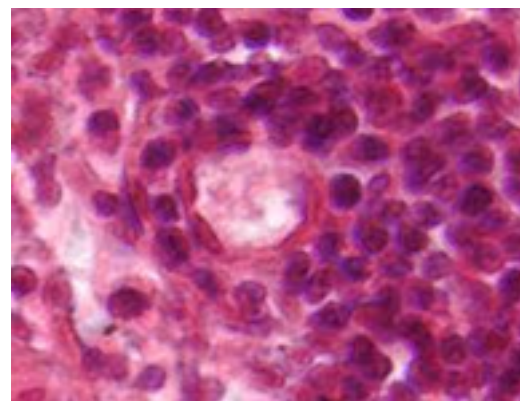
The solution to this problem should be carried out by a phased combination of the reproduction of diabetic nephropathy and the application of burn wounds to the cortical layer of the kidneys. For morphological studies, tissue samples in the form of pieces of kidney tissue were taken by performing an operation under ether anesthesia.

## RESULTS

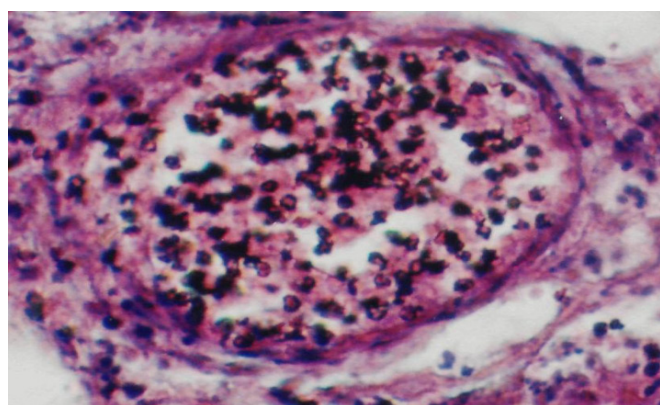
The first variant of the dynamic study were models with diabetic nephropathy. With a 5-day period of diabetes mellitus, mild symptoms of diabetic nephropathy were noted, which were based on microangiopathies (Figure 2). They were manifested by some increase in proliferation and swelling of arteriole endothelial cells, and areas of plasma impregnation of their walls, mainly in the subendothelial zones with plasma proteins, detected in the form of small foci. Swelling of endotheliocytes in places was accompanied by destructive changes in some of them. Occasionally there was perivascular edema and mild lymphohistiocytic infiltration around individual arterioles. On the 10th day of observation in the capillaries and venules, along with the phenomena of congestive plethora, with a tendency to hemolysis, there was a thinning of the walls of the vessels containing in the lumen, in addition to erythrocytes, many neutrophils (Figure 3).



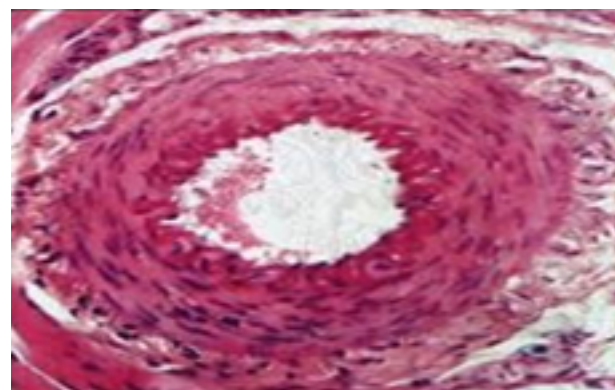
**Figure 2:** 5-day diabetic nephropathy; Swelling of arteriole endotheliocytes with their destructive changes, perivascular edema and weak lymphohistiocytic infiltration. Hemotoxylin and eosin, 400 times magnification.



**Figure 4:** Day 30 of modeling diabetic nephropathy; Plethora of capillaries with signs of their thrombosis and adhesion of erythrocytes to the basement membrane. Hemotoxylin and eosin, 400 times magnification.



**Figure 3:** 10-day diabetic nephropathy; Plethora of blood vessels with the presence of many lymphocytes and neutrophilic leukocytes. Hemotoxylin and eosin, 400 times magnification.

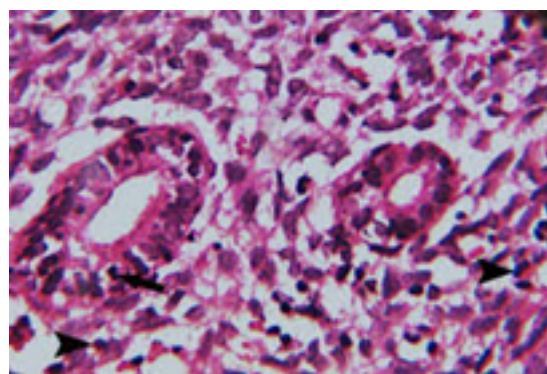


**Figure 5:** 30 simulations of diabetic nephropathy; Plasma impregnation, swelling and desquamation of endotheliocytes. The site of thinning and destruction of the wall of arterioles, Hemotoxylin and eosin. 400 times magnification.

On the 20<sup>th</sup> day of reproduction of diabetic nephropathy, morphologically, more significant violations of most capillaries and arterioles were noted, compared with those of the previous observation period. They were manifested in a pronounced swelling of endothelial cells, flattening of the nuclei with a thickening of their basement membrane, and in some cases, their desquamation into the lumen of the vessels. Plasma impregnation with fixation of plasma components in the subendothelium was noted in the vessel wall. In addition to thickening of the basement membranes in arterioles, thickening of their layers and the presence of pericytes in small vessels, as well as smooth muscle cells in arterioles, were observed. The connective tissue surrounding the blood vessels showed edema and perivascular infiltration.

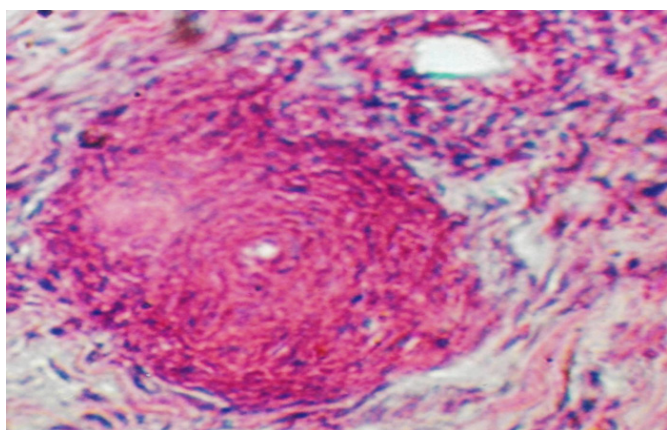
On the 30<sup>th</sup> day of reproduction of diabetic nephropathy, the lumens of small vessels looked wide with signs of congestive plethora. Some of them were in a state of thrombosis (Figure 4). Arterioles and venules were characterized by changes in blood cells in the form of adhesion of erythrocytes to the surface of endotheliocytes, and in some places, to the basement membrane. In addition to the narrowing of the lumen of individual arterioles, due to thickening of the walls, because of plasma impregnation, swelling and desquamation of endothelial cells into their lumen, there were areas of thinning of the walls (Figure 5) with the release of erythrocytes.

The venules were characterized by an enlarged lumen and a pronounced perivascular infiltration. The 40-day period of modeling diabetic nephropathy was manifested by a pronounced swelling of endothelial cells, their hypertrophy, destruction, detachment from the basement membrane, as well as their rejection into the lumen of the vessel (Figure 6).

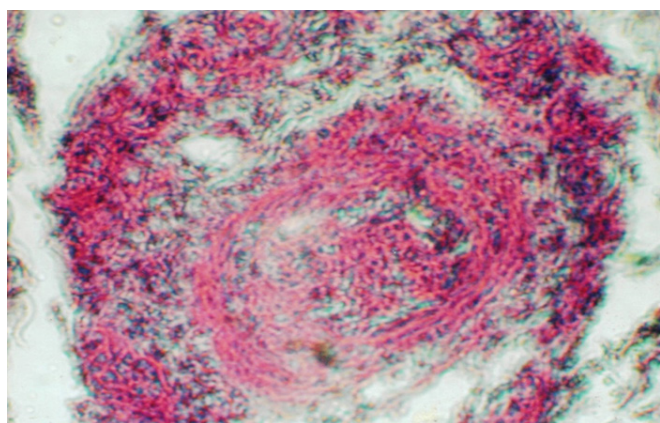


**Figure 6:** 40-day simulation of diabetic nephropathy; Swelling of the endothelium, their hypertrophy, detachment from the basement membrane, destruction of the vessel walls. Hemotoxylin and eosin, 400 times magnification.

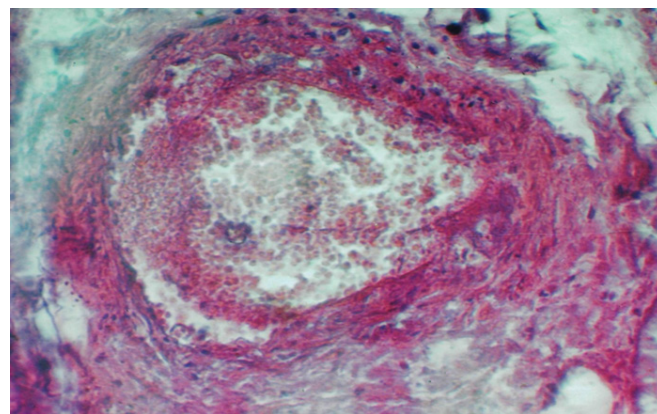
Sometimes, the processes of pericytes or smooth muscle cells were immersed in the formed gaps. The noted thickening of the walls of most arterioles was accompanied by hyalinosis of their walls, which was both segmental and circulatory in nature. More significant, in comparison with the early periods of observation, plasma impregnation of vessel walls was revealed, moreover, it was observed in all layers. Significant thickening of the walls of arterioles occurred mainly due to an increase in the thickness of the basement membrane of endotheliocytes. In some cases, its profusion into the lumen of the vessel was determined, leading, together with the above changes, to its significant narrowing or complete obliteration (Figure 7). In separate observations, on the 50<sup>th</sup> day of modeling, recalibration was detected in arterioles, leading to the appearance of “vasa vasorum” (Figure 8). In the late terms of the experiment (60-80 days), while maintaining all the above morphological signs of microangiopathy, phenomena of complete loss of the endothelial lining by hyalinized vessels are noted. In view of this, they were represented by cell-free tubules, the lumen of which was filled with accumulations of erythrocytes, with the occurrence of thrombosis. These periods were characterized by significant disturbances in the blood cells the phenomena of hemolysis, and areas of thrombosis. As a result, there was a redistribution of erythrocytes to the surface of endotheliocytes (Figure 9).



**Figure 7:** 40-day simulation of diabetic nephropathy; Hyalinosis, thickening of the arteriole wall with a sharp narrowing of the lumen (obliteration). Hemotoxylin and eosin, 400 times magnification.



**Figure 8:** 50-day diabetic nephropathy; The phenomenon of pericollimation with the appearance of “vasa vasorum”. Hemotoxylin and eosin, 400 times magnification.



**Figure 9:** 60-day simulation of diabetic nephropathy; Hyalinosis of the wall of arterioles with the complete absence of the endothelial layer, the phenomenon of hemolysis of erythrocytes with their location at the basement membrane. Hemotoxylin and eosin, 400 times magnification.

In addition to the accumulation of erythrocyte aggregates resembling the shape of mulberries, swollen, and torn off from the basement membrane, endotheliocytes clogged the lumen of the vessels. At the same time, in some cases, a pronounced proliferation of connective tissue was observed perivascularly, forming a kind of connective tissue “clutch”.

The results of our morphological studies in the dynamics from 5 to 80 days of modeling diabetic nephropathy indicate the development of diabetes mellitus with its complication, the manifestation of which was the presence of its most characteristic indicator of vascular damage in the form of various degrees of microangiopathy. It was noted that the severity of pathomorphological changes in blood vessels was directly dependent on the duration of the process. Characteristically, all structural components of the vascular wall were subjected to changes in experimental diabetes.

In the dynamics of the reproduction of diabetes mellitus with diabetic nephropathy throughout the 80-day duration of the disease, in accordance with the stages of microangiopathy, we identified 3 periods of its pathomorphological changes:

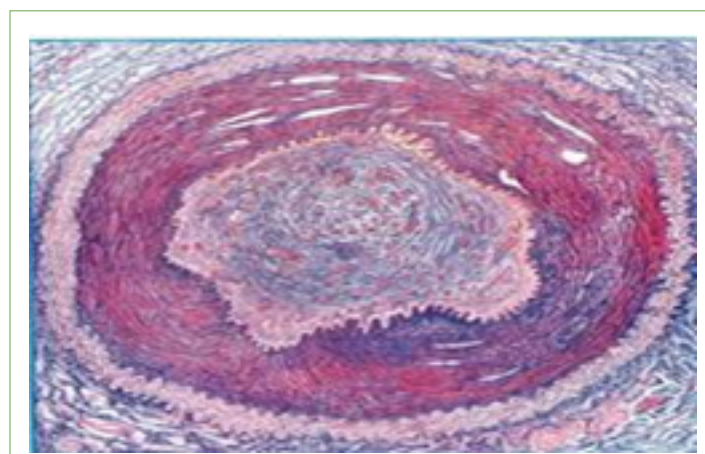
I period up to 10 days was characterized by mild signs of angiopathy in the form of swelling of the endothelium of arterioles, slight impregnation of their walls with plasma protein, light, perivascular infiltration, and edema in the form of congestive plethora. Thinning of the capillary walls was observed.

In the II period of experimental modeling (20-30 days), the progression of the process was noted, manifested in deeper structural changes in most vessels. In addition to plasma impregnation of subendothelial sections of arterioles, proliferation of endothelial and perithelial cells, as well as their desquamation, narrowing of the lumen due to thickening of the walls was observed. There was also an expansion of the lumen of small vessels, their stagnant plethora, infiltration of adventitia layers.

III period (40-80 days) was characterized by a more significant development of morphological signs of diabetic microangiopathy. Along with the morphological changes identified in the early stages, the phenomenon of hyalinosis of most arteriole walls, as well as their pronounced plasma impregnation, was noted. Swelling and detachment of endotheliocytes with the introduction of smooth

muscle cells into the vessel wall with their percalibration and the formation of vasa vasorum, as well as a significant narrowing of the lumen of arterioles. At the same time, perivascular edema, infiltration, and proliferation of connective tissue were observed. Changes in blood cells were manifested in their tendency to hemolysis, adhesion of the luminal surface, the appearance of erythrocyte aggregates with the development of thrombosis. At the same time, pronounced damage to endotheliocytes, their detachment from the basement membrane led to an increase in the lumen of arterioles, and the reaction of smooth muscle cells and pericytes contributed to the thickening of the basement membranes. Prolonged plasma impregnation causes the development of hyalinosis of microvessels.

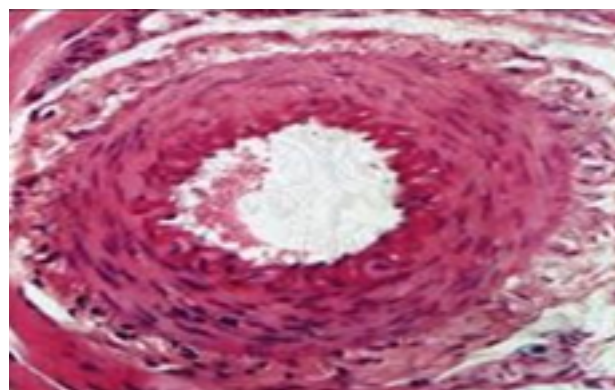
Continuation of experimental studies showed that the application of burn wounds to the cortical layer of the kidneys in the arteries revealed fibrinoid disorganization of collagen with hyalinosis phenomena. There was a lack of an internal elastic membrane in damaged endothelium. At the same time, the middle shell in these areas was thinned. Throughout the vessel, calcifications were encountered, between which areas of inflammation were determined, sometimes with the transition of their fibrosis. In the adventitia associated with vessels, there are signs of productive vasculitis and obliteration of the lumen, as well as the presence of vasa vasorum with a circular thickening of its intima (Figure 10). In the subsequent periods after the application of burn wounds, in general, the same type of angiogenic changes characteristic of nephropathy were revealed, some of which turned out to be deeper, such as stenosing sclerosis, as well as fibrosis of the tunica media. In the adventitium layer, along with vasculitis vasa vasorum, there are lymphohistiocytic infiltrates, indicating the phenomena of focal periarteritis. In adjacent thickenings of the intima with the phenomena of fibrosis, as well as signs of vasculitis.



**Figure 10:** Simulation of chronic renal failure on the background of diabetic nephropathy. Arteriole wall thickening, hyalinosis, plasma impregnation, perivascular edema. Hemotoxylin and eosin, 400 times magnification.

By the 60<sup>th</sup> day of modeling chronic renal failure against the background of diabetic nephropathy, a pronounced stenosis and thickening of the intima of the artery of a circular nature were characteristic. It noted the phenomena of hyperplasia and fibrosis of connective tissue structures, as well as muscle fibers. The expansion of the collateral structures of the capillary network of muscle tissue had no increase in the luminal area (Figure 11). Based on the foregoing, it follows that when modeling diabetic nephropathy by a combined chemical method, all elements of the vascular wall of the

kidneys undergo structural changes. At the same time, the degree of their violation in angiopathy is directly dependent on the duration of the experiment.



**Figure 11:** 60-day modeling of chronic renal failure on the background of diabetic nephropathy. Hyperplasia and fibrosis of connective tissue structures. Hemotoxylin and eosin, 200 times magnification.

The 3 stages of nephropathy identified by us during the experiment (I-minor, II-moderate and III-severe) testified to the choice of terms for modeling chronic renal failure. The main criteria for a possible period of transition from nephropathy to the development of chronic renal failure is the presence of hyalinosis of microvessels with thickening of the membranes, which indicated the occurrence of irreversible angiogenic changes. This period is defined by us as 40 days of modeling diabetic nephropathy.

## DISCUSSION

According to a few authors, diabetes mellitus refers to metabolic-vascular diseases, called diabetic microangiopathy. [ For it, the most characteristic morphological features are thickening of the basement membranes of varying severity, plasma impregnation, hyalinosis of the capillary walls and arterioles, narrowing of the lumen of the vessels, proliferation of endothelial cells, perithelial cells, their destruction and rejection, changes in the rheological properties of blood [11-13]

The morphological characteristics of chronic renal failure against the background of diabetic nephropathy is characterized by the development of glomerulosclerosis and proteinuria. In response to a decrease in the functioning renal mass as a result of burn wounds, structural and functional hypertrophy of the remaining glomeruli occurs. The diameter of the renal glomeruli increases due to dilatation of glomerular capillaries, extracellular matrix deposition, and cell proliferation. Hypertrophied proximal tubules increase in diameter and length. There is an infiltration of the deep structures of the renal tissue with myofibroblasts, deposits of interstitial collagens, and tubulointestinal fibrosis develops [11-15].

It is known that glomerular and tubulointerstitial sclerosis is caused not only by increased synthesis of extracellular matrix components, but also by their reduced degradation. According to the data of a few authors obtained on the model of subtotal nephrectomy, the level of cysteine and metalloproteinases is reduced both in the renal glomeruli and in the proximal tubules [16,17].

Infiltration of the interstitium with inflammatory cells is a characteristic feature of many chronic kidney diseases. Infiltrating

cells contribute to renal tissue fibrosis through several mechanisms: leukocytes synthesize oxygen radicals and pro-inflammatory cytokines that damage renal tissue; lymphocytes and macrophages are the source of profibrinogenic molecules such as TFR-b, oFRF, platelet growth factor, which in turn activate fibroblasts and stimulate epithelial-mesenchymal transdifferentiating. In contrast, nephrocyte growth factor reduces inflammation in the renal glomeruli and tubulointerstitial, suppresses the expression of MCR-1 and RANTES, and reduces fibrosis of renal tissue in a model of chronic renal failure [18-20].

## CONCLUSION

Damage to the microvascular bed, followed by hypoxia and ischemia of the renal tissue, plays an important role in the development of chronic renal failure in a model with diabetic nephropathy. At 1-2 weeks from the onset of the disease, proliferation of glomerular and peritubular endothelial cells increases, the length and number of capillaries of the renal glomeruli increase, i.e., active angiogenesis is noted. This process stimulates vascular endothelial growth factor (VEGF), the production of which by podocytes is increased. But then, at 4-8 weeks, a progressive decrease in the number of glomerular and peritubular capillaries develops due to the loss of endothelial cells under the action of oxidants, angiotensin II, FAS, and an inadequate response to angiogenic stimuli. Both the lack of expression of the angiogenic factor VEGF by podocytes and tubular epithelial cells and the increased expression of the antiangiogenic factor thrombospondin-1 in the renal glomeruli and interstitium play a certain role in the disruption of angiogenesis. Thrombospondin-1 inhibits the proliferation of endothelial cells stimulated by VEGF and oFRF, causing their apoptosis. As a result, the density of glomerular and peritubular capillaries decreases, glomerulosclerosis and interstitial fibrosis develop.

## ETHICAL CLEARANCE

All experimental studies were reviewed, discussed, and approved by the bioethical committee of the Ministry of Health of the Republic of Uzbekistan and fully complied with the terms of the 1986 Council of Europe Convention for the Protection of Animals.

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