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# CLINICAL EXPERIMENTAL DYNAMICS OF RENAL PARENCHYMAL AND MICROCIRCULATORY VEIN DAMAGE IN TRANSIENT ARTERIAL HYPERTENSION AS A RESULT OF DIABETES

**Khatamov Vokidjon Bakhtiyorovich**
Central Asian Medical University

**Abstract.** Arterial hypertension in the setting of diabetes mellitus creates a complex of mutually reinforcing (synergistic) pathogenic factors that accelerate damage to the renal parenchyma and microcirculatory system. Hyperglycemia “fragile” the capillary network through endothelial dysfunction, glomerular hyperfiltration, oxidative stress and inflammation, while arterial hypertension increases intraarterial hypertenial pressure, deepens arteriolar remodeling, hyalinosis and ischemia. As a result, in the early stages, functional reversible disorders (albuminuria, hyperfiltration, impaired microcirculatory autoregulation) predominate, and then irreversible structural changes such as nodular glomerulosclerosis, tubulointerstitial fibrosis, loss of peritubular capillaries and renal failure are formed. This article discusses the time dynamics of these processes in clinical observations and experimental models, modern biomarkers, treatment strategies, and the relevance of the problem based on Uzbek and world statistics.

**Keywords:** diabetes mellitus, arterial hypertension, diabetic nephropathy, glomerular hyperfiltration, albuminuria, endothelial dysfunction, SGLT2 inhibitors, finerenone.

## Introduction

Today, the diabetes-hypertension “pair” is one of the largest risk clusters, dramatically increasing not only cardiovascular complications, but also the burden of chronic kidney disease (CKD). The global prevalence of diabetes has reached 11.1% among adults (20–79 years) and is expected to increase sharply by 2050, increasing the pressure on health systems . The updated WHO facts on hypertension predict that by 2024, 1.4 billion adults aged 30–79 years will have hypertension, a significant proportion of whom will have controlled hypertension. CKD, as a result of major studies based on the Global Burden of Disease 2023 analysis, has once again shown that it is a "silent epidemic", with 788 million adults affected by it in 2023, the age-standardized prevalence among adults reaching 14.2%, and CKD rising to 9th place among the causes of global death in 2023 (1.48 million deaths).

The problem is also very relevant in Uzbekistan: the IDF Atlas data indicate that in 2024 the number of people aged 20–79 living with diabetes in Uzbekistan is approximately 1.5 million, and it is projected to reach 2.2 million by 2050. The WHO Uzbekistan country-fact sheet and STEPS materials on hypertension indicate that the prevalence among adults is around ~38% (the assessment methodology may differ in different sources).

In practice, the combination of diabetic nephropathy (DN) and arterial hypertension is dangerous due to the faster onset of albuminuria, accelerated decline in eGFR, and early progression to end-stage renal failure (need for dialysis/transplantation). Analysis of arterial hypertension, nephrology and hemodialysis services in Uzbekistan for 2019–2024 noted that the number of patients registered with diabetic nephropathy has increased over the years (the source may be qualitatively heterogeneous, but it signals a trend).

The development of arterial hypertension and damage to the renal parenchyma/microcirculatory system in diabetes mellitus occurs sequentially and simultaneously through the triad of “pressure + metabolic toxicity + microangiopathy”. To understand the process in clinical and experimental dynamics, it is convenient to distinguish time-dependent stages such as

1) early functional phase
2) subclinical structural phase

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3) clinically manifest DN/CKD phase

4) late fibrotic–ischemic phase.

First of all, the glomerular microcirculation is very sensitive to arterial hypertension and diabetes. The balance of the tone of the afferent and efferent arterioles in the glomerulus determines the intraarterial hypertonic-lumenular pressure. In the early stages of diabetes, increased $Na^+$–glucose reabsorption (SGLT2 pathway) weakens tubuloglomerular feedback through the macula densa, causing afferent vasodilation and hyperfiltration in superficial arterial hypertension; in addition, when arterial hypertension is added, the intraarterial hypertonic-lumenular pressure “doubles” and mechanical stress on the capillary wall increases.

At this stage, the patient may still have “normal” creatinine, but hemodynamic fluctuations associated with microalbuminuria, nocturnal/morning pressure elevation, arterial pressure variability, and heart rate appear. At the microscopic level, thinning of the endothelial glycocalyx, NO biodeficiency, endothelin-1 activation, and uneven capillary perfusion are observed.

Microangiopathy of diabetes mellitus is characterized by thickening of the basement membrane in the microcirculatory system, impaired pericyte function, increased capillary permeability, and “stickiness” of proteins/erythrocytes to microvessels (impaired hemorheology).

Arterial hypertension, on the other hand, causes media thickening, lumen narrowing, and hyaline arteriolosclerosis in arterioles, reducing the flow to the glomerulus and peritubular capillaries. The result is paradoxical: on the one hand, the pressure in the glomerular capillaries is high (hyperfiltration), and on the other hand, ischemia in the tubulointerstitial zone increases. This “glomerulotubular imbalance” subsequently becomes one of the main drivers of tubulointerstitial fibrosis and decreased EGFR.

To better understand the clinical-experimental dynamics, experimental models are used: streptozotocin (STZ)-induced type 1 diabetes model, db/db or ob/ob (obese-insulin-resistant) type 2 diabetes model, salt-sensitive hypertension models (e.g., SHR or angiotensin II infusion) and their combinations.

Combined models (diabetes mellitus + arterial hypertension) are closer to the “real” phenotype of human arterial hypertension, showing a more rapid deterioration of microcirculatory autoregulation, albuminuria and glomerulosclerosis. In the early weeks–months (e.g., 4–12 weeks), glomerular hyperfiltration, afferent arteriole dilatation, oxidative stress markers (NADPH oxidase activity), inflammatory cytokines (TNF- α , IL-6), podocyte damage (decreased nephrin/podocin expression) are detected; Later (3–6 months) there is an increase in mesangial matrix expansion, nodular foci, tubulointerstitial infiltration, and grade I/III accumulation of collateral arterial hypertension.

The central link in the “microcirculatory core” of this process is endothelial dysfunction. The endothelium is not only a “cover”, but also an active endocrine organ: NO, prostacyclin, endothelin, adhesion molecules (VCAM-1, ICAM-1), which controls thrombogenicity.

Under conditions of hyperglycemia, advanced glycation end-products (AGE) and their receptors (RAGE) are activated, triggering inflammation and fibrosis through the NF- κ b pathway. Arterial hypertension, in turn, increases shear stress and increases the “tearability” of the endothelium. Therefore, in the combination of diabetes mellitus + arterial hypertension, microangiopathy is not only rapid, but also “diffuse”: along with the glomerular capillaries, peritubular capillaries also disappear (capillary rarefaction).

If peritubular perfusion decreases, hypoxia in tubular cells (HIF pathways), mitochondrial dysfunction, and then fibrosis increase. This results in clinical signs such as "not just albuminuria" - but also elevated tubular markers (KIM-1, NGAL, L-FABP), casts in the urine, and decreased concentration ability.

Morphologically, diabetic glomerulosclerosis (Kimmelstiel–Wilson nodes) and mesangial matrix expansion are classic findings. The histological example given above in the

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arterial hypertension carousel describes the diabetic appearance of diabetic glomerulosclerosis with PAS staining (narrowing of the capillary lumen, nodular proliferation of the matrix).

In this case, in the presence of arterial hypertension, the proportion of hyalinosis of arterioles, thickening of the intima–media in interlobular arteries, and global glomerulosclerosis is higher. In clinical and experimental dynamics, it is this "arteriolopathy" that paves the way for ischemic remodeling of the renal parenchyma: the number of glomeruli decreases, and the remaining nephrons perform compensatory hyperfiltration, which creates a "vicious cycle" that accelerates the process itself.

Another important pathway leading to exacerbation is the renin–angiotensin–aldosterone system (RAAS). Angiotensin II further constricts the efferent arteriole, increasing intraarterial hypertension and pulmonary arterial pressure; aldosterone, in turn, increases inflammation and fibrosis. Therefore, RAAS blockade (ACE inhibitors/ARBs) remains the "mainstream" strategy in the combination of DN and arterial hypertension and diabetes mellitus.

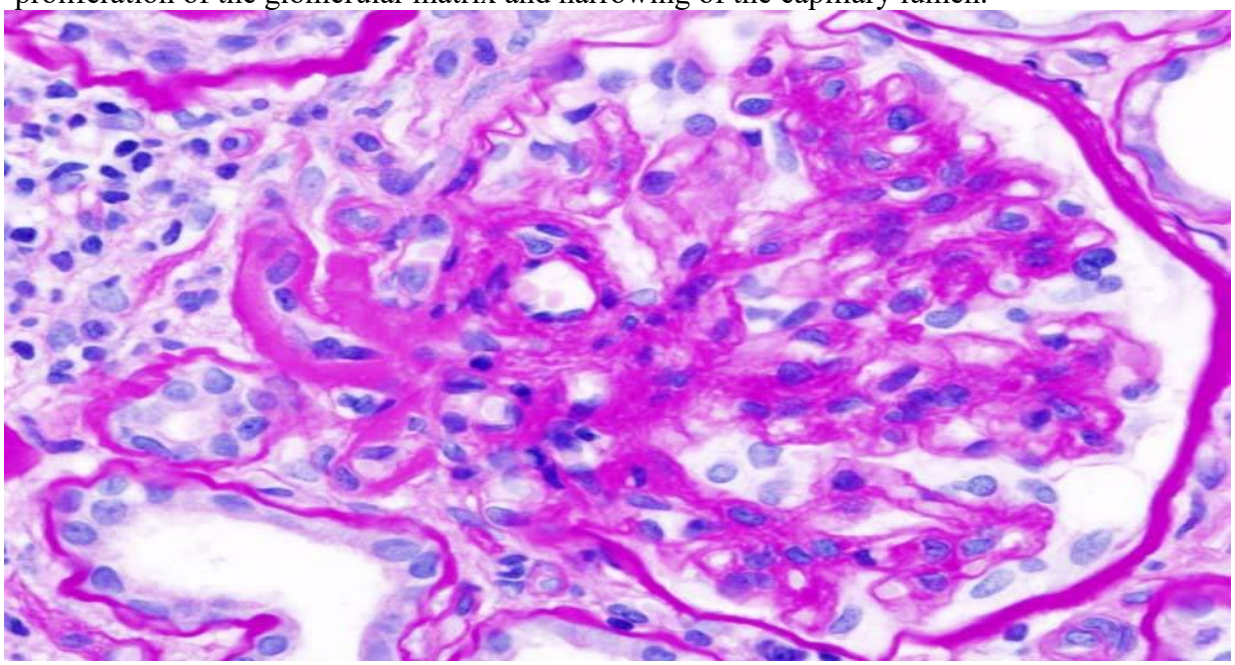
However, in recent years, the paradigm of renoprotection has expanded: the KDIGO 2024 CKD guidelines and the ADA 2025 documents on diabetic CKD emphasize SGLT2 inhibitors as one of the main drug classes for slowing CKD progression and reducing cardiovascular risk in patients with eGFR above a certain threshold; There is also evidence that the mineralocorticoid receptor antagonist finerenone, an antihypertensive agent, has a positive effect on renal and cardiovascular outcomes (especially in patients with T2DM+CKD and albuminuria).

In the context of "World News", global approaches to CKD and hypertension in 2024–2025 will be strengthened in two directions: (1) population screening (albuminuria/serum creatinine/eGFR and blood pressure control), (2) increasing the level of control (access to treatment, drug supply, protocolized approach).

The WHO 2025 news emphasizes that the level of hypertension control is still low in many countries, and the disease remains undiagnosed in a large population. For CKD, a large analysis based on GBD 2023 data in 2025 showed a sharp increase in the burden of CKD, with 788 million adults having CKD in 2023, and CKD rising to 9th place.

These data reinforce the need to bring the "QD + AG + CKD" triad of prevention and early intervention to the level of public policy.

**Figure 1.** Histological appearance of diabetic glomerulosclerosis (PAS stain) — nodular proliferation of the glomerular matrix and narrowing of the capillary lumen.



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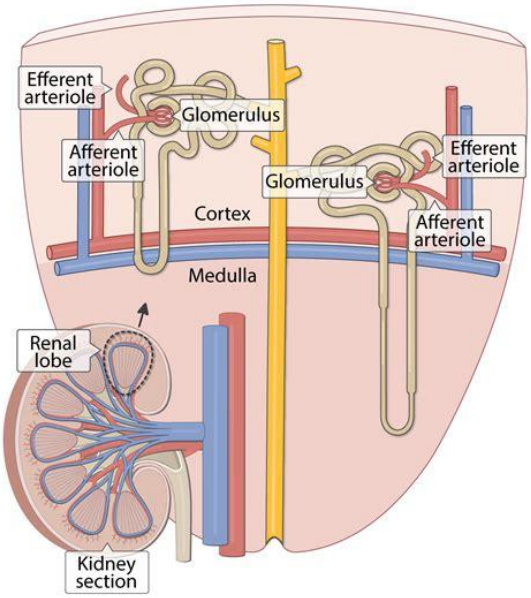
In Uzbekistan, the clinical picture is often similar to that of arterial hypertension: type 2 diabetes (often with obesity, dyslipidemia), parallel or subsequent arterial hypertension, and then an increase in the urinary albumin/creatinine ratio (UACR), a slow decrease in eGFR, fundus microangiopathy, left ventricular hypertrophy, peripheral artery disease.

Given the estimated number of people living with diabetes in the country in 2024 at around 1.5 million (IDF) and the prevalence of hypertension at ~38%, it is natural that the combination of "diabetic nephropathy + hypertension" will increase the burden on nephrological services. Some regional observations provide figures on CKD and the need for dialysis (for example, separate lists are provided for Karakalpakstan and Andijan).



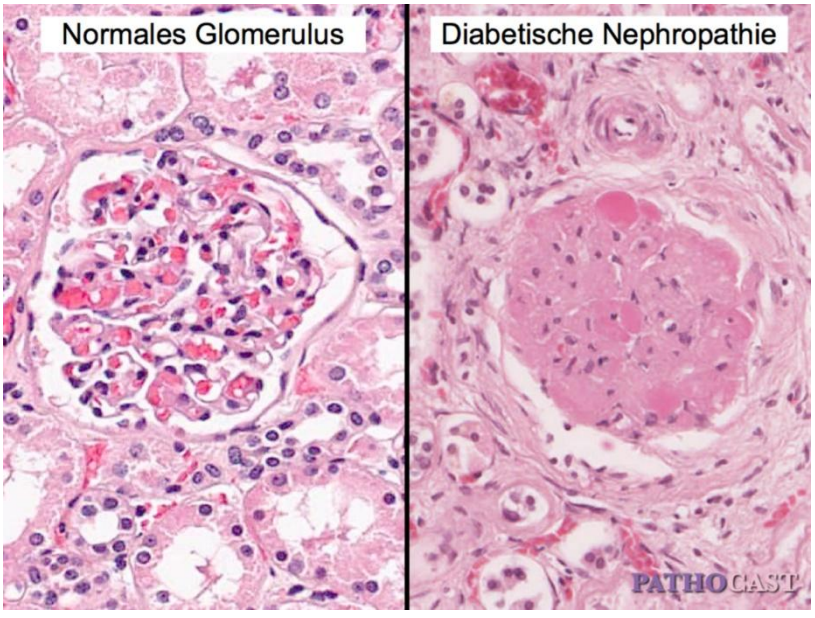

However, to manage clinical-experimental dynamics, not only the "late stage" (dialysis), but also early screening (UACR and EGFR) and the diurnal blood pressure profile (ABPM), glucose variability, lipids, smoking, and obesity require aggressive control of arterial hypertension.

The following table summarizes the typical dynamics of renal parenchymal and microcirculatory damage in a patient with arterial hypertension on the background of diabetes mellitus (as well as in an experimental model). (The time interval may be years in the clinic, months in the experiment; however, the sequence is similar.) the clinical "visible" aspect of microcirculatory damage is albuminuria and decreased eGFR, in practice the type of arterial hypertension (systolic/diastolic, pulse pressure, evening elevation), its variability and "masked hypertension" (normal in the office, high at home) strongly determine the dynamics of DN.

Therefore, regular ABPM (24-hour monitoring) and home measurements, as well as individual determination of target blood pressure values (age, comorbidities, orthostatic risk) are important. The KDIGO 2024 CKD guidelines highlight blood pressure control and proteinuria reduction in people with CKD as a central focus for slowing CKD progression.

**Figure 2.** Schematic of the renal nephron and glomerular afferent/efferent arterioles (for the concept of microcirculatory flow).

In the experimental model, morphology (histology), immunohistochemistry (collar arterial hypertension, α -SMA, TGF- β ), electron microscopy (podocyte footpad effacement), microcirculation perfusion (laser doppler, intravital microscopy), and oxidative stress markers (MDA, SOD, catalase) are evaluated together to accurately monitor the "dynamics".




In the clinic, less invasive markers such as UACR, egfr (CKD-EPI), cystatin C, urine NGAL/KIM-1, blood pressure profile, glycemic control (hba1c), lipids, fundus angiopathy, cardiac EHO (LVH) provide an "integral" assessment. The ADA

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2025 documents clearly indicate the role of SGLT2 inhibitors and other classes in the management of CKD and cardiovascular risk in patients with diabetes.

**Figure 3.** Comparative histology of a healthy glomerulus and a glomerulus in diabetic nephropathy.

The clinical-experimental dynamic effect of treatment on arterial hypertension is also very time-dependent: measures such as stable glucose control (individual HbA1c target), weight loss, salt restriction, physical activity, and smoking cessation reduce microcirculatory endothelial stress in the early stages.

In the case of arterial hypertension, RAAS blockade reduces intraarterial hypertension and glomerular pressure, thereby reducing albuminuria. In recent years, the concept of "metabolic + hemodynamic" renoprotection has gained momentum: SGLT2 inhibitors have gained a strong place in many recommendations, as they reduce glomerular hyperfiltration, reduce albuminuria, and slow the progression of CKD.

There is also a large clinical evidence base and subsequent reviews/analyses for finerenone (T2DM+CKD), which notes a positive effect on albuminuria and renal-CV endpoints.

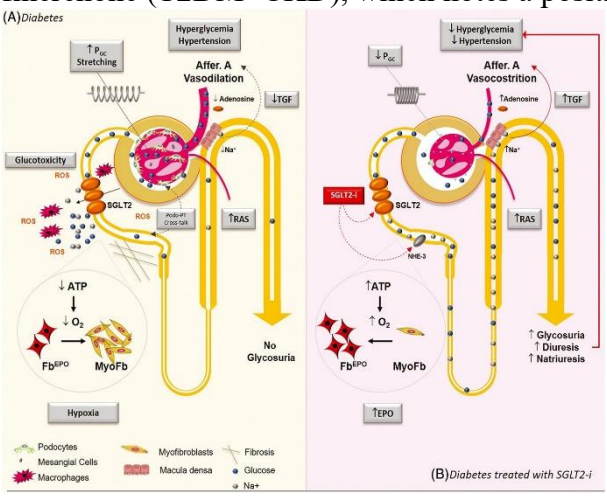


**Figure 4.** Pathophysiological conceptual diagram related to SGLT2 inhibition (hyperfiltration and fibrosis pathways).

It should be noted separately: microcirculatory damage is often "multi-organ". Diabetic retinopathy, peripheral neuropathy, cerebral microangiopathy can occur in parallel with DN. Therefore, in clinical practice, it is advisable to assess the general microangiopathic phenotype (fundus, neurological examination of the legs, heart and vessels), and not "kidney separately". Especially in Uzbekistan, where the prevalence of diabetes mellitus is predicted to increase (IDF), it is important to strengthen screening and early renoprotection protocols at the primary level.

Global statistics support this trend: hypertension is expected to affect 1.4 billion adults by 2024, with the majority of them in low- and middle-income countries. In countries with weak laboratory screening (UACR), continuous drug supply, and blood pressure management protocols, the burden of DN and CKD will accelerate. With CKD estimated to affect 788 million adults and cause 1.48 million deaths by 2023, major estimates of arterial hypertension also call for "early management of risk factors": diabetes, hypertension, and obesity.

**Conclusion.**

Arterial hypertension in the setting of diabetes mellitus is a powerful pathogenic combination that accelerates damage to the renal parenchyma and microcirculatory system, creating a continuous chain of progression from early-stage arterial hypertension functional disorders (hyperfiltration, microalbuminuria, endothelial dysfunction) to late-stage arterial hypertension irreversible fibrosis-ischemia and ESD.

When considering the combined clinical and experimental dynamics, it appears that impaired microcirculatory system autoregulation, peritubular capillary rarefaction, and tubulointerstitial fibrosis are the "main drivers" of the decrease in EGF. Given the increasing global burden of diabetes (IDF 2025), hypertension (WHO 2025), and CKD (GBD 2023-based arterial hypertension 2025 analyses), the estimated number of people living with diabetes in Uzbekistan to be around 1.5 million in 2024, and the high prevalence of hypertension, managing the problem with early screening (UACR/egfr), ABPM, lifestyle modification, and evidence-based renoprotective therapy (RAAS blockade, SGLT2 inhibitors, finerenone/GLP-1RA in appropriate cases) should be a priority.

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