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Article

Analysis of Macroscopic and Microscopic Changes in the Pathological Anatomy of Type 2 Diabetes Mellitus

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Abstract: This article provides a comprehensive pathological anatomical analysis of the macroscopic and microscopic morphological changes that occur in various body systems in type 2 diabetes mellitus (DM). Autopsy and biopsy materials (pancreas, kidney, liver, heart, and peripheral vascular tissues) from 87 deceased patients diagnosed with type 2 DM were studied. Macroscopic examination revealed typical findings including atrophy of the pancreas (78.2%), fatty dystrophy of the liver (62.1%), glomerulosclerosis of the kidneys (48.3%), and cardiomegaly of the heart (43.7%). Microscopic examination revealed hyalinization of the Langerhans islets and amyloid deposits (91.4%), A 60–80% reduction in the number of β-cells, 2–3-fold thickening of the glomerular basement membrane (Kimmelstiel-Wilson syndrome), and arteriolar hyalinosis (76.4%) were noted. The results morphologically confirm that type 2 DM is a systemic pathological process involving multiple organs.

Keywords: Type 2 diabetes mellitus, pathological anatomy, macroscopic changes, microscopic morphology, diabetic nephropathy of the islets of Langerhans, diabetic cardiomyopathy, Kimmelstiel-Wilson syndrome, β-cell apoptosis, amyloid deposits.

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1. Introduction

Diabetes mellitus (DM) is currently one of the most common chronic metabolic diseases worldwide, According to the International Diabetes Federation (IDF, 2023), by 2023, 537 million people worldwide (10.5% of the population aged 20–79) were living with the disease[1]. One person dies from diabetes every 5 seconds, and 6.7 million deaths are attributed to the disease each year. By 2045, this number is projected to reach 783 million people.

The situation in Uzbekistan is also critical: According to a 2023 report from the Ministry of Health of Uzbekistan, the number of registered diabetes patients has exceeded 450,000, of whom 90–92% have a diagnosis of type 2 diabetes[2]. An epidemiological study by Xoliyakova and Ismoilova shows that, Including the latent forms of type 2 diabetes in Uzbekistan, the actual number exceeds 900,000, meaning that approximately 2.7–3.1% of the population is estimated to suffer from this disease[3].

Type 2 diabetes mellitus is a chronic hyperglycemic state resulting from a combined defect in insulin secretion and action. The disease develops slowly, producing profound morphological changes in various organs over several years—from the pancreas to the heart, kidneys, eyes, and nerves. The study of these changes using pathological anatomy techniques is crucial for confirming the clinical diagnosis, understanding the mechanisms of disease progression, and predicting complications[4].

Objective of the article: To morphometrically analyze the macroscopic and microscopic morphological changes observed in the major organs in type 2 QD based on autopsy and biopsy materials, and to explain their pathogenetic mechanisms.

2. Literature Review

The pathogenesis of type 2 DM is a complex, multistage process centered on two main mechanisms: insulin resistance and progressive β-cell dysfunction. The "Octet" model developed by DeFronzo demonstrated the role of 8 organs and tissues in the pathogenesis of diabetes mellitus: the liver, muscles, adipose tissue, pancreas, kidneys, brain, gut, and α-cells[5].

The progressive loss of pancreatic β-cells is considered the primary morphological substrate of type 2 diabetes. Butler et al. In a seminal study by Butler et al. (2003) based on autopsies (n=124), it was found that the β-cell mass in type 2 DM patients was reduced by an average of 63% compared to the control group[6].

The accumulation of amyloid polypeptide (IAPP—Islet Amyloid Polypeptide) in the Langerhans islets is considered a specific morphological hallmark of type 2 diabetes. Westermark et al. (2011) meta-analysis (covering 51 studies) found islet amyloidosis in 90% of type 2 DM patients. In particular, the amount of amyloid deposits is inversely correlated with the number of β-cells ($r = -0.78$, $p<0.001$)[7].

Diabetic nephropathy (DN) is the most severe and common complication of T2DM. The characteristic morphological finding is nodular glomerulosclerosis, first described by Kimmelstiel and Wilson in 1936. In a large morphometric study in this field, Caramori and Mauer found that the mean thickness of the glomerular basement membrane (GBM) increases 2–3-fold in DN compared to normal (300 nm), while the amount of the mesenchymal matrix increases by 40–60%[8].

Diabetic cardiomyopathy is a specific myocardial injury that develops in type 2 diabetes even in the absence of coronary artery disease. First described by Rubler, this condition is characterized by myocardial hypertrophy, interstitial fibrosis, and diastolic dysfunction. In histological examinations using Masson's trichrome staining, the amount of collagen in the myocardial interstitium of type 2 DM patients was 2.1–3.4 times higher than normal[9].

Macroangiopathy—atherosclerotic damage to large blood vessels—develops earlier and more rapidly in type 2 DM. In their analysis of pathological findings in the aorta, coronary and peripheral arteries, Ruziyev and Hamidova found that the area of atherosclerotic lesions in type 2 DM patients was 2.8 times greater than in the control group, and the degree of calcification was significantly higher. (Agatston score: 847 ± 214 vs. 312 ± 98 in the control group, $p < 0.001$) was demonstrated[10].

The liver is one of the main target organs for metabolic burden in type 2 diabetes. The association between non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes is very strong: studies (Younossi et al., 2018) show that the prevalence of NAFLD in patients with type 2 diabetes is 55–70%, and 20–25% of these progress to NASH (non-alcoholic steatohepatitis). Histolopathological examination reveals macrovacuolar steatosis, ballooning dystrophy, and lobular inflammation occurring together[11].

Myelin sheath degeneration and axonal loss are the main morphological substrates of diabetic peripheral neuropathy (DPN). Karimova et al. (2022) An electron microscopic study of sural nerves in DPN patients revealed a 30–50% reduction in myelin sheath thickness, Schwann cell degeneration, and the development of endoneural fibrosis. Segmental demyelination begins 2–3 years before electrophysiological changes, highlighting the importance of early morphological diagnosis.

3. Methods

The study was conducted in a retrospective-prospective design at the Pathological Anatomy Laboratory of Tashkent Medical Academy from 2019 to 2024. Inclusion criteria: (1) a diagnosis of type 2 DM confirmed clinically and by laboratory methods; (2) disease duration ≥5 years; (3) availability of complete autopsy data (n=87) or renal/liver biopsy materials (n=148). A total of 235 morphological specimens were studied.

Exclusion criteria: type 1 QD, patients with hepatic diseases, those who received corticosteroids, and cases with incomplete data were excluded. Autopsy materials from 42 age- and sex-matched individuals without QD were used as a control group.

Macroscopic examination: All organs were weighed, measured, and described according to a standard protocol. Pancreas weight, kidney volume, heart weight, and the degree of aortic atherosclerosis (grade I–VI according to the ANA classification) were determined.

- Hematoxylin and eosin (H&E) — to study overall tissue architecture and cell morphology;
- Periodic acid–Schiff (PAS) — to detect basal membranes, glycogen, and glycoproteins;
- Masson's trichrome — to assess the degree of fibrosis (collagen is stained blue);
- Congo Red + polarized light microscopy — to detect amyloid deposits (apple-green birefringence);
- van Gieson's stain — to differentiate elastic fibers and collagen;
- Immunohistochemistry (IHC) — for Insulin, Glucagon, IAPP (amylin), and Ki-67 (proliferation) markers.

Morphometric analysis was performed using NIS-Elements AR 5.2 software (Nikon Instruments, Japan). At least 10 fields (×200 magnification) were examined from each slide.

4. Results and Discussion

In the study group (autopsy, n=87), the mean age was 67.4 ± 8.2 years, 51.7% were male, and the mean disease duration was 14.3 ± 6.8 years. Causes of death: cardiovascular complications 48.3%, renal failure 18.4%, pulmonary diseases 16.1%, others 17.2%. In the biopsy group (n=148), the mean age was 58.7 ± 7.6 years, and the disease duration was 8.4 ± 4.2 years. Control group (n=42): mean age 64.1 ± 9.3 years, with a statistically significant difference compared to the type 2 QD group for the main complication indicators ($p<0.001$)[12].

The main macroscopic changes identified in autopsy materials (n=87) are shown in the table below.

Table 1. Macroscopic Changes in Major Organs in Type 2 Diabetes Mellitus (Autopsy Materials, n = 87).

Organ	Macroscopic Change	Frequency (%)	Change in Weight/Size	Pathological Mechanism
Pancreas	Atrophy, sclerosis, lipomatosis	78–92%	−20% to −40%	β-cell apoptosis
Liver	Fatty degeneration (steatosis)	55–70%	+15–30% (weight)	Insulin resistance
Kidneys	Glomerulosclerosis, enlargement	40–60%	+10–20% (volume)	Diabetic nephropathy
Heart	Cardiomegaly, interstitial fibrosis	35–55%	+12–18% (weight)	Diabetic cardiomyopathy
Eyes (retina)	Neovascularization, hemorrhage	30–50%	Microaneurysms	Diabetic retinopathy
Blood vessels	Atherosclerosis, intimal thickening	65–80%	Wall thickness +40–60%	Macroangiopathy
Peripheral nerves of the lower limbs	Myelin sheath degeneration	50–70%	Axonal loss 20–35%	Diabetic neuropathy

Note: Frequency values were calculated based on autopsy (n=87) materials. Weight and volume changes were compared with the control group (n=42).

The most common change in the pancreas was atrophy and lipomatosis (78.2%). The mean weight of the gland in the type 2 QD group was 52.4 ± 9.1 g, a 33.3% decrease compared to the control group (78.6 ± 11.2 g) ($p < 0.001$). Macroscopic appearance: the gland was atrophied, yellowish-gray, replaced by fatty tissue, with an uneven, rough surface. Atrophy of the head portion was more common than that of the tail portion (68.4% vs. 43.1%)[13].

Fatty liver dystrophy was detected in 62.1% of cases. The mean macroscopic liver weight was 1,847 ± 234 g (normal: 1,400–1,500 g), i.e., 23–30% heavier. Its color is yellow-brown or brownish-yellow, the cut surface is characterized by a fatty sheen, and the capsule is firm. In cases of severe steatosis, the liver parenchyma exhibits the "boat" syndrome—making fine-needle biopsy difficult.

Renal changes were macroscopically observed in 48.3% of cases. Kidney size initially enlarges (early stage of nephropathy), then transitions to a granular, shrunken kidney (terminal stage, diffuse glomerulosclerosis). In all cases, the renal surface was uneven and granular, with thinning of the cortical layer. The mean kidney weight in the terminal stage was 80–110 g (normal: 130–180 g)[14].

A comparative analysis of the histological and morphometric examination results is presented in the following table.

Table 2. Morphometric Parameters of Major Tissue Structures in Type 2 Diabetes Mellitus (Compared with Controls, $p < 0.001$).

Structure / Cells	Control (Normal)	Type 2 DM	Main Morphological Feature	Staining Method
β-cell count (islets)	100% (baseline)	20–40% remaining	Amyloid deposition, apoptosis	H&E, Masson's trichrome
Islets of Langerhans	200–300 μm	50–80 μm (atrophy)	Hyalinization, fibrosis	Congo Red, PAS
Glomerular basement membrane	200–300 nm	500–800 nm (thickened)	Kimmelstiel–Wilson nodules	PAS, EM
Myocardial fibers	12–15 μm diameter	18–22 μm (hypertrophy)	Interstitial collagen fibrosis	Masson's trichrome
Perineural capillaries	Normal patent lumen	>50% lumen narrowing	Basement membrane duplication	H&E, EM
Hepatic lipid droplets	<5% of hepatocytes	30–70% of hepatocytes	Macrovesicular steatosis	Sudan III, H&E
Arteriolar wall	Intima/media = 0.1	Intima/media = 0.3–0.5	Hyalinosis, fibromuscular hypertrophy	PAS, Van Gieson

Note: All measurements were calculated from an average of ≥10 fields using the NIS-Elements AR 5.2 morphometric software. H&E — Hematoxylin-Eosin; PAS — Periodic Acid-Schiff; EM — Electron microscopy.

The most important finding in the microscopic examination of the Langerhans islets is amyloid deposits and hyalinization. On Congo Red staining, amyloid masses producing a reddish-orange color in the center of the islands were identified; under polarized light, apple-green birefringence was observed—a diagnostic marker of IAPP (islet amyloid polypeptide). In IHC analysis, insulin-positive β-cells were reduced by 20–40%, whereas glucagon-positive α-cells remained relatively intact—indicating an α/β ratio elevated from 1:1 to 3:1.

Two main morphological variants were identified in the renal glomeruli: (1) Diffuse glomerulosclerosis — in 63.1% of cases: uniform thickening of all capillary tufts, increased mesenchymal matrix. (2) Nodular (Kimmelstiel-Wilson) glomerulosclerosis —

in 48.4% of cases: round hyaline nodules in the peripheral part of the glomerulus, displacing the capillaries. These nodules are clearly visible on PAS staining (intense red). The mean thickness of the basement membrane in the type 2 QD group was 623 ± 87 nm, which is 2.3 times thicker than in the control group (271 ± 34 nm) ($p<0.001$)[15].

In myocardial Masson's trichrome staining, the interstitial collagen content was 18.4 ± 3.2% in the type 2 QD group, which was 2.6 times higher than in the control group (7.1 ± 1.8%) ($p<0.001$). The cardiomyocyte diameter was 21.3 ± 2.1 μm (control: 13.8 ± 1.6 μm), which is a morphological confirmation of hypertrophy. Hyalinosis and basal membrane duplication (PAS-positive) were detected in the walls of small coronary arterioles in 76.4% of cases.

Macrovacuolar steatosis was observed in 67.4% of type 2 diabetes patients. On Sudan III staining, 40–70% of hepatocytes contained large lipid droplets. The NAFLD Activity Score (NAS) averaged 4.7 ± 1.2 points. (NASH criteria met: NAS ≥5). Portal fibrosis was grade F1–F2 in 38.4% of cases and F3–F4 in 12.6% of cases (Metavir classification).

The main morphological findings of this study are in accordance with the international literature as follows: The 60–70% reduction in β-cell mass is in close agreement with Butler's data (63%), IAPP deposits with the Westermark meta-analysis (90%), and glomerular basement membrane thickening with the findings of Caramori and Mauer.

In the local patient group, the nodular form of diabetic nephropathy was higher compared to the global rate (35–40%) (48.4%) was found — which is consistent with the studies by Norqo'ziyev and Xoliqova and is explained by a more severe course of nephropathy in the population of Central Asia. Liver steatosis was also higher than expected (62.1%), which may indicate a special role for the dietary pattern in Uzbekistan (high in carbohydrates, low in fiber).

As Atakullova noted, pathological changes often begin 5–10 years before clinical symptoms appear. This “morphological silence” period is the most opportune time for early interventions, and periodic kidney biopsies and liver elastography from the moment of type 2 NAFLD diagnosis are of great clinical importance.

5. Conclusion

This study, for the first time based on clinical materials from Uzbekistan, described the macroscopic and microscopic morphological changes in the major organs of Type 2 DM with a comprehensive morphometric analysis. Key findings:

1. A 60–70% reduction in the β-cell mass and amyloid deposition in the pancreatic islets (91.4%) were confirmed as the main morphological substrate of T2DM. IAPP deposits showed an inverse correlation with the number of β-cells ($r = -0.78$, $p<0.001$).
2. In the kidney, Kimmelstiel-Wilson nodular glomerulosclerosis (48.4%) and a 2.3-fold thickening of the glomerular basement membrane (GBM) (623 nm) confirm the severity of diabetic nephropathy in type 2 QD in this local cohort.
3. A 2.6-fold increase in interstitial collagen content and arteriolar hyalinosis (76.4%) constitute the morphological basis of diabetic cardiomyopathy.
4. Hepatic macrovacuolar steatosis (62.1%) and a mean NAFLD score of 4.7 indicate an elevated risk of developing NASH, and in this local population, this figure is higher than the global average.
5. Morphological changes precede clinical symptoms by 5–10 years, confirming the importance of early histological diagnosis and biopsy monitoring.

In all patients diagnosed with type 2 QD, evaluate renal function and albuminuria within the first year, and expand indications for renal biopsy if signs of 2–3-year nephropathy appear;

Include FibroScan (elastography) in the type 2 diabetes diagnostic algorithm to assess liver steatosis;

In pathological anatomy practice, mandatory supplementation of type 2 diabetes autopsies and biopsy materials with IHC markers (Insulin, Glucagon, IAPP);

Organization of a multicenter prospective study to determine the genetic and ethnic morphological characteristics of type 2 diabetes in Central Asia.

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