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MORPHOLOGICAL EVALUATION OF PULMONARY INTERSTITIAL FIBROSIS IN EXPERIMENTAL ANIMALS WITH ALLOXAN-INDUCED TYPE I DIABETES MELLITUS

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Noncommunicable Diseases (NCDs) – primarily cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes – are the leading causes of death worldwide. More than **36 million people die from NCDs every year** (accounting for **63% of all global deaths**), of whom **14 million die prematurely**, i.e., before the age of 70.

Low- and middle-income countries currently bear about **80% of this burden of premature mortality**, which is largely **preventable** and linked to four main risk factors: **tobacco use, unhealthy diets, physical inactivity, and harmful use of alcohol**.

If current trends continue, experts project that by **2030**, the NCD epidemic will claim **52 million lives annually**. This situation poses a threat not only to global health but also to development and economic growth.

NCDs cause **losses in national income** amounting to **billions of dollars**, and due to rising healthcare costs, **millions of people fall below the poverty line** every year. For all countries, the **cost of inaction far outweighs the cost of intervention**, with **developing countries suffering the most**.

The adoption of the **WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases** at the **66th World Health Assembly** marked a **turning point** in addressing this major global public health challenge. We now have effective strategies to **prevent and treat NCDs**.

The **Global Action Plan** serves as a **roadmap** for **Member States** and other stakeholders, providing a **range of policy options**, **interventions**, and a **monitoring framework**. Member States can choose policy options based on their specific context and available resources.

The package of measures in the action plan includes **cost-effective interventions** that can be implemented **sustainably in all countries** with **moderate increases in resources**.

In addition, the **25 indicators** included in the **global monitoring framework** can be **adapted to the national context** to assess progress toward the **voluntary global targets**.

The **Global Action Plan** has the **potential to reverse the NCD trend**. If implemented in collaboration with **Member States**, other **UN agencies**, **NGOs**, and the **private sector**, it can

help achieve **nine voluntary global targets**, including **a 25% reduction in premature NCD mortality by 2025**.

The **drivers of the rapid rise** in NCD burden and their risk factors – such as **globalized marketing and trade, urbanization, poverty, and population aging** – are **universal**. Populations in **low- and middle-income countries** are **much less protected** from NCD risks and consequences than populations in **high-income countries**, where people are generally shielded by **national policies and strategic plans**.

Moving forward, a **more integrated approach** is necessary to close this gap and provide **developing countries** with **policy guidance, technical support, and capacity-building assistance**.

Based on this Action Plan, **WHO** is leading the way in promoting **effective and cost-efficient interventions** and will continue to **support countries in their implementation**. Even **simple actions** – such as **reducing salt in food products**, **offering affordable medications** to prevent lung disease, heart attacks, and strokes, or **increasing tobacco taxes** – can have a **transformative impact**.

We look forward to **collaborating with countries** to **save lives**, **improve health and well-being** for current and future generations, and **prevent the humanitarian, social, and financial burden of NCDs** from undermining past **development achievements**.

Pulmonary interstitial fibrosis (PIF) in diabetes mellitus is considered one of the major causes of disability and mortality across the world, including in Uzbekistan. It contributes significantly to economic and social burdens, with its incidence increasing each year. Globally, PIF ranks fourth among causes of death.

The main patient population comprises individuals of working age (40–67 years). Severe disease progression, frequent hospitalizations, disability, and mortality are often associated with comorbid conditions, one of the most prevalent being diabetes mellitus (DM).

Diabetes mellitus is a major medical and social issue due to its high prevalence, chronic course, high rates of disability, and mortality from complications. According to the latest WHO data published in 2020, diabetes-related deaths in Uzbekistan reached 6,205 cases, accounting for 3.84% of total mortality. The age-standardized death rate is 25.78 per 100,000 population, placing Uzbekistan 96th globally.

According to official statistics, the number of registered patients with diabetes mellitus in Uzbekistan is 202,998. Among them, 17,662 have type 1 diabetes, including 2,033 children and 817 adolescents. The number of patients with type 2 diabetes is 185,336.

Among diabetic patients, mortality from cardiovascular diseases and stroke is 2–3 times higher, blindness occurs 10 times more frequently, nephropathy is 10–15 times more prevalent, and gangrene of the limbs is 20 times more common compared to the general population [1].

In recent years, the prevalence of combined PIF and DM has increased due to longer life expectancy and the age-related rise in both conditions. According to various authors, the coexistence of DM and PIF ranges from 2% to 35.8%. Comorbidity in PIF is a critical issue in modern medicine. In the management and treatment strategies of patients with PIF and concurrent DM, it is essential to consider the risk factors and mechanisms underlying the

development and progression of both diseases.

PIF is currently viewed as a preventable and treatable condition. It is characterized by persistent airflow limitation, which typically progresses and is associated with a pronounced chronic inflammatory response of the lungs to pathogenic particles or gases. In some patients, exacerbations and comorbidities significantly impact the severity of PIF [7].

The etiology of PIF is closely linked to risk factors such as genetic predisposition, inhalational exposures, lung growth and development, oxidative stress, sex, age, respiratory infections, past tuberculosis, socioeconomic status, and comorbidities. In 80–90% of PIF cases, smoking is the primary risk factor. A direct correlation has been established between smoking and the annual decline in forced expiratory volume in one second (FEV_1). In healthy, non-smoking individuals over the age of 35, the average decline is about 30 mL per year, and clinically significant pulmonary obstruction rarely develops. In smokers, including passive smokers, airway obstruction of varying degrees develops, which may eventually become disabling or fatal.

Although smoking cessation does not restore FEV_1, it may normalize the rate of its decline. A 10% decrease in FEV_1 increases cardiovascular mortality by 28% and the risk of non-fatal coronary events by 20% in patients with mild to moderate PIF [13].

PIF is a polygenic disease and exemplifies gene–environment interactions. Alpha-1 antitrypsin deficiency is a rare inherited disorder, inherited in an autosomal recessive manner, most frequently observed among individuals of Northern European descent [7].

Alpha-1 antitrypsin deficiency leads to early-onset panlobular emphysema and PIF, and disease onset is accelerated by smoking. Various genes may participate in PIF pathogenesis, including those encoding transforming growth factor beta 1 (TGF-β1), microsomal epoxide hydrolase-1 (mEPHX-1), and tumor necrosis factor alpha (TNF-α).

Chronic inflammation plays a central role in the progression of PIF. Its pathogenesis includes oxidative stress, proteolytic tissue destruction, immune deficiency, and microbial colonization.

In the early stages of PIF, these pathogenetic factors are activated by external risks, but as the disease becomes established, the process becomes self-perpetuating. Inflammation affects all layers of the bronchial wall, lung parenchyma, and pulmonary vessels, leading to key manifestations of chronic obstructive pulmonary disease (COPD): pulmonary emphysema, airway remodeling, and peribronchial fibrosis [4, 5].

Etiological factors activate almost all cellular components in the respiratory system. The primary roles are played by neutrophils, macrophages, and lymphocytes. These cells release mediators that enhance the inflammatory response (pro-inflammatory cytokines such as TNF-α and interleukins) and induce structural changes (e.g., TGF-β) [2]. This promotes interaction between inflammatory and structural cells in the airways and lung parenchyma.

Smoking leads to a tenfold increase in the concentration of neutrophils in the distal parts of the respiratory system (RS) [40]. Neutrophils play a key role in mucus hypersecretion and the release of proteases. An increase in the number of CD4+ and CD8+ T lymphocytes is observed in the airway walls and pulmonary parenchyma, with an elevated CD8/CD4 ratio. CD8+ cells exert cytotoxic effects on alveolar cells, contributing to their destruction.

Activated inflammatory cells (neutrophils and macrophages) release large amounts of free radicals, which possess potent damaging effects. Smoking is an exogenous source of oxidants,

including oxygen, ozone, peroxides, and hydroperoxides. Pulmonary antioxidant defense consists of enzymatic systems (such as superoxide dismutase [SOD] and glutathione) and non-enzymatic components (vitamins E, C, β-carotene, uric acid, flavonoids, and bilirubin) [3, 7, 12].

Oxidants exert direct toxic effects on the structural components of the lungs (DNA, lipids, proteins, connective tissue); they enhance the synthesis of mucus glycoproteins by epithelial cells, damage mucociliary transport and fibroblasts, stimulate thromboxane formation, reduce surfactant activity, and contribute to endothelial dysfunction. Oxidants also inactivate protease inhibitors, facilitating the destruction of alveolar walls and extracellular membranes by elastase, which further stimulates the synthesis of pro-inflammatory interleukins. Thus, disruption of the oxidant-antioxidant balance plays a crucial role in the pathogenesis of interstitial pulmonary fibrosis (IPF).

Persistent inflammation in IPF is associated with a range of systemic manifestations that impact patient survival and the development of comorbidities. These include cachexia, skeletal muscle loss, increased cardiovascular risk, anemia, osteoporosis, and depression.

Endothelial status is currently a widely studied topic in chronic obstructive pulmonary disease (COPD). In COPD, inflammation is a persistent process that exerts constant detrimental effects on the endothelium. Risk factors for endothelial damage include hypercholesterolemia, hyperhomocysteinemia (HHcy), and elevated levels of cytokines (IL-1β, TNF-α, IL-8). Exposure of the vascular endothelium to aggressive factors leads to its activation, initially as a protective mechanism. Prolonged exposure results in three stages of endothelial activation:

1. Primary activation of synthetic intracellular processes;
2. Secondary disruption in the sequence and balance of these processes;
3. Cellular depletion and destruction.

In modern literature, the latter two stages are characterized as **endothelial dysfunction** [17].

One of the most potent vasoconstrictors—angiotensin II—is formed via activation of the renin-angiotensin system. The role of the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of COPD and in the development of pulmonary hypertension and chronic cor pulmonale (CCP) is now well established. Elevated levels of angiotensin II and aldosterone stimulate vascular smooth muscle cell proliferation, vasoconstriction, and increased blood volume—factors that initiate and maintain the pathological mechanisms leading to CCP. Angiotensin II also exerts **profibrotic and pro-inflammatory** effects, contributing to vascular remodeling in the pulmonary circulation.

In 1999, the World Health Organization (WHO) defined diabetes mellitus (DM) as a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycemia in DM leads to damage, dysfunction, and failure of various organs—particularly the eyes, kidneys, nerves, heart, and blood vessels [11].

Risk factors for type 2 diabetes mellitus (T2DM) are conventionally divided into two groups:
– **Modifiable (external)** factors: excess body weight and obesity (especially abdominal obesity), physical inactivity, and high-calorie diets.
– **Non-modifiable (internal)** factors: older age, impaired intrauterine development, and genetic predisposition [4, 10, 11, 15].

The key pathogenic mechanisms underlying T2DM include **insulin resistance (IR)**, defective insulin secretion, reduced incretin effect, glucagon secretion abnormalities, hepatic glucose overproduction, and glucotoxicity [10].

Insulin resistance is defined as a diminished biological response of peripheral tissues to endogenous or exogenous insulin. In Italy, the prevalence of IR among people aged 40–79 is reported as follows:
– 10% among those without metabolic disorders,
– 58% in individuals with arterial hypertension,
– 63% with hyperuricemia,
– 84% with hypertriglyceridemia,
– 88% with low HDL cholesterol,
– 84% with T2DM.

It is known that **tumor necrosis factor-alpha (TNF-α)** reduces insulin sensitivity in adipose and muscle tissues, although the mechanisms underlying IR are still being investigated [1, 8]. While IR and β-cell dysfunction may initially develop independently, they eventually interact to trigger hyperglycemia and associated glucotoxicity.

IR may affect various organs and tissues, contributing both to glucotoxicity and increased cardiovascular risk. In patients with T2DM, cardiovascular mortality is 3–4 times higher than in those without metabolic disorders. A direct correlation exists between the degree of IR and the severity of abdominal obesity, coagulation system activation, blood lipid atherogenicity, and carotid artery wall thickness in both diabetic and non-diabetic individuals [10, 11, 14].

Recent studies have identified local RAAS components in adipose tissue and the pancreas. RAAS plays a role in the development of visceral obesity and diabetes. The **diabetogenic role of RAAS** is linked to the effects of angiotensin II on insulin secretion and insulin resistance. Activation of tissue RAAS components contributes to diabetes complications, including **decreased thromboresistance**, increasing the risk of thrombotic events.

Currently, oxidative stress is recognized as a key factor in the progression of diabetes mellitus [11]. Oxidative stress is induced by hyperglycemia (via protein glycation and the binding of advanced glycation end products [AGEs] to the proteins of vascular basement membranes). The action of free radicals initiates mechanisms of β-cell damage and reduces nitric oxide synthesis. Superoxide and hydroxyl radicals initiate the oxidation of low-density lipoproteins (LDL). Peroxide-modified LDLs possess greater atherogenic potential, can damage the vascular endothelium, and accumulate in the subendothelial space.

Mitochondrial dysfunction has attracted considerable scientific interest. In diabetes, dysfunctional mitochondria tend to overproduce reactive oxygen species (ROS), leading to increased oxidative stress and the activation of protein kinase C. Thus, mitochondrial dysfunction is directly linked to endothelial dysfunction.

Endothelial dysfunction plays a central role in the pathogenesis of vascular complications in type 2 diabetes mellitus (T2DM). Hyperglycemia, insulin resistance, elevated free fatty acids, oxidative stress, and other metabolic changes associated with diabetes contribute to the development of endothelial dysfunction and, consequently, to the initiation and progression of atherosclerosis. The vascular endothelium functions as an integrated endocrine organ that regulates vascular tone and permeability, maintains hemostatic and fibrinolytic balance, and modulates inflammation, resolution, and tissue repair through the synthesis of various mediators. Many researchers have noted a correlation between endothelial health and the course of various

diseases [9]. According to several authors, endothelial dysfunction presents specific features in the context of combined respiratory diseases, including infections, and diabetes mellitus [16].

Currently, the comorbid pathology of chronic obstructive pulmonary disease (COPD) and diabetes is being actively investigated. In cases where these diseases coexist, structural and functional changes in the endothelial cells of alveolar capillaries have been observed. Endothelial dysfunction progresses more rapidly due to the reciprocal negative impact of each condition. Chronic hyperglycemia perpetuates pathological processes in the endothelium, leading to early and severe complications of diabetes and accelerating the progression of interstitial lung fibrosis (ILF). Additionally, persistent systemic inflammation contributes to further detrimental changes in endothelial function. The syndrome of mutual aggravation results in the rapid progression of endothelial dysfunction. These factors negatively affect the condition of patients with COPD and diabetes, leading to early disability and increased mortality rates.

Therefore, systemic inflammation in ILF contributes to metabolic imbalance in the body, promotes insulin resistance, and the development of T2DM, highlighting ILF's significant role in the pathogenesis of type 2 diabetes. T2DM further stimulates the secretion of pro-inflammatory cytokines, promotes oxidative stress and endothelial dysfunction, which in turn sustains chronic inflammation in the respiratory tract and fosters the progression of both COPD and diabetes, along with their complications. A "vicious cycle" emerges from the bidirectional aggravating effects of COPD and type 2 diabetes. Understanding the etiopathogenetic aspects of this comorbidity allows for a personalized approach to managing patients with COPD and T2DM.

In recent years, non-infectious upper respiratory tract pathologies, particularly interstitial lung fibrosis, have become increasingly linked to endocrine system disorders, especially type 1 diabetes mellitus (T1DM). T1DM is a chronic condition with a consistent upward trend in incidence. It is associated with a high risk of early disability and reduced life expectancy due to the development of vascular complications and loss of functional activity in vital organs and systems.

The early onset typical of T1DM, often in childhood or young adulthood, significantly lowers the age at which complications appear. The only reliable means of preventing adverse outcomes is through adequate metabolic control, aimed at maintaining blood glucose levels as close to physiological norms as possible [1]. It is important to note that the harmful effects of hyperglycemia on somatic health, development, and vascular risks are observed not only in T1DM but in all forms of diabetes, including gestational diabetes [2].

The criteria for compensation in type 1 diabetes mellitus (T1DM) have been repeatedly revised, with a trend toward bringing the recommended glycemic targets closer to physiological levels. According to the latest revision of the International Society for Pediatric and Adolescent Diabetes (ISPAD, 2018) and the national clinical guidelines on type 1 diabetes in children (2019), the target for glycemic control in T1DM is a glycated hemoglobin (HbA1c) level below 7% [3,4].

However, as stated in the resolution of the scientific advisory council on the use of intermittently scanned continuous glucose monitoring technology, "current approaches to managing diabetes mellitus should include not only glycemic control but also minimization of hypoglycemia risks and reduction of glucose variability" [5]. It is well known that the treatment of T1DM is multifaceted and includes not only replacement insulin therapy, but also regulation of diet, physical activity, and the formation of a specific lifestyle for patients with chronic illness.

Overview of Respiratory Diseases and Diabetes in the CIS and Uzbekistan. The overall situation concerning respiratory diseases and type 1 diabetes mellitus in the CIS countries and

Uzbekistan mirrors global trends and is characterized by an increasing medical and social burden of these widespread chronic diseases, particularly among the aging population. Environmental changes worldwide have led to a rise in the frequency of interstitial lung lesions associated with type 1 diabetes mellitus.

In recent years, there has been a noted increase in interstitial lung involvement complicated by the presence of diabetes. The presence of diabetes mellitus aggravates the course of interstitial lung disease, worsens the prognosis, and is often the cause of fatal outcomes. This necessitates a deeper study of pathogenesis, the identification of risk factors for the development of lung fibrosis in diabetes, and the development of early diagnostic criteria, improved treatment methods, and preventive measures.

Objective of the Study. To perform a morphological assessment of interstitial lung fibrosis development in rats with alloxan-induced diabetes.

Materials and Methods. The study was conducted on 30 rats with alloxan-induced diabetes, which was induced via three subcutaneous injections of alloxan at a dose of 170 mg/kg. A control group consisted of 6 intact rats. On the 60th day of the experiment, the rats were decapitated under light ether anesthesia. Samples of lung and pancreatic tissue were fixed in 10% neutral formalin, decalcified initially in EDTA solution, followed by nitric acid. The tissues were then processed using standard histological procedures with a carousel-type tissue processor (STP 120, Thermo Fisher Scientific, USA), and embedded in paraffin.

Sections 5–6 μm thick were obtained using a rotary microtome (HM 325, Thermo Fisher Scientific, USA) and stained with hematoxylin-eosin and Masson's trichrome for histological examination under a light microscope (Axio Lab.A1, Carl Zeiss, Germany).

Results. Morphological studies of the pancreas in intact rats showed uniform staining with preserved lobular architecture. The acini, Langerhans islets, excretory ducts, and arteries of the pancreas displayed typical structure [Fig. 1].

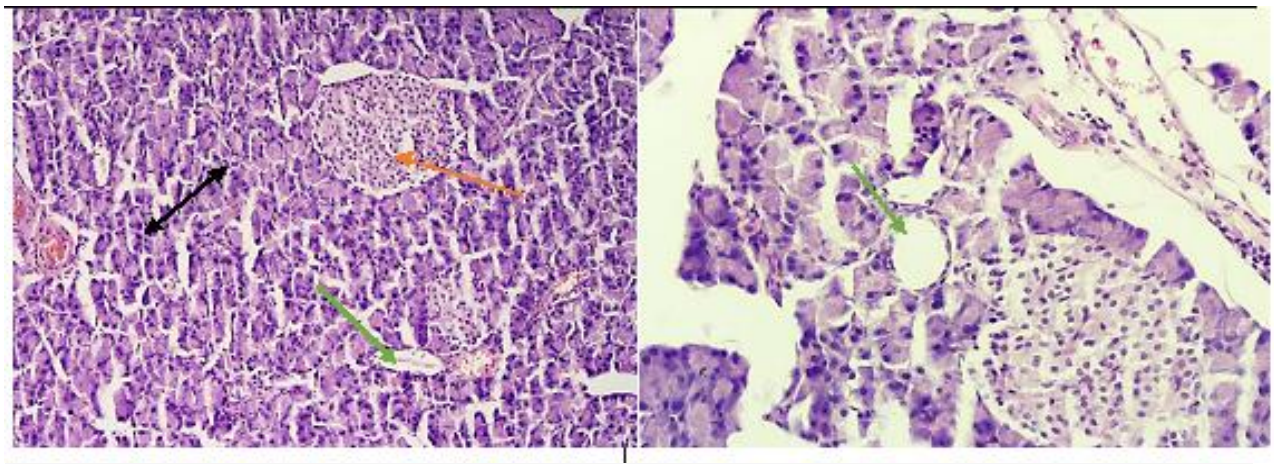
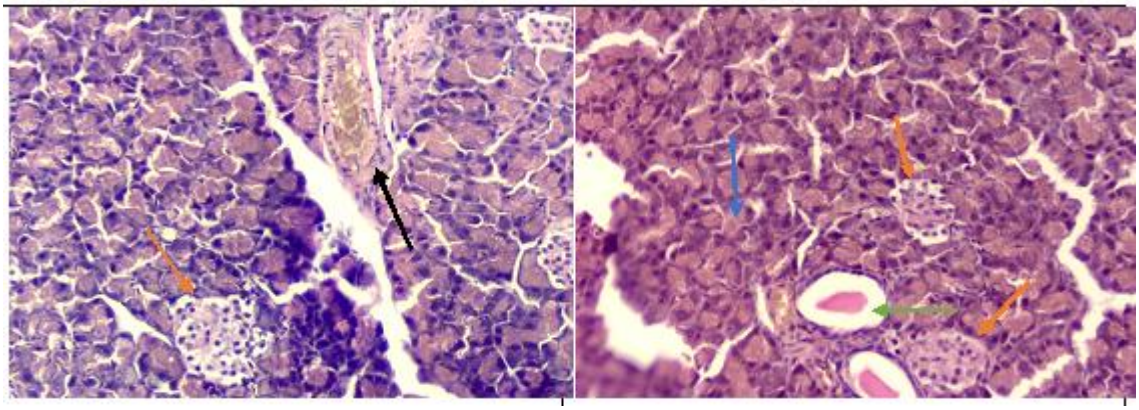


Fig. 1. Pancreas with preserved lobular structure. Acini (double arrow) of normal size, Langerhans islets (orange arrow), excretory ducts (green arrow), and pancreatic arteries with typical structure. Stain: H&E. Magnification ×100 (left) and ×200 (right).

Morphological studies of the pancreas in experimental rats revealed reduced pancreatic islets (orange arrow) with vacuolated cells, acinar cells with hypoplasia (blue arrow), and marked thickening of the blood vessel walls (black arrow).



[Fig.2].
Fig. 2. Reduced pancreatic islets (orange arrow) with vacuolated cells, acinar cells with hypoplasia (blue arrow), and marked thickening of the blood vessel walls (black arrow). Excretory ducts with lumen dilation and signs of obliteration by proteinaceous material (green arrow). Stain: H&E. Magnification ×100 (left) and ×200 (right).

Morphological studies of the lungs in intact rats showed unchanged pulmonary acini composed of single-layered cuboidal flattened epithelium. Blood vessels appeared normal, with no wall thickening or signs of hyperemia observed. [Fig. 3]

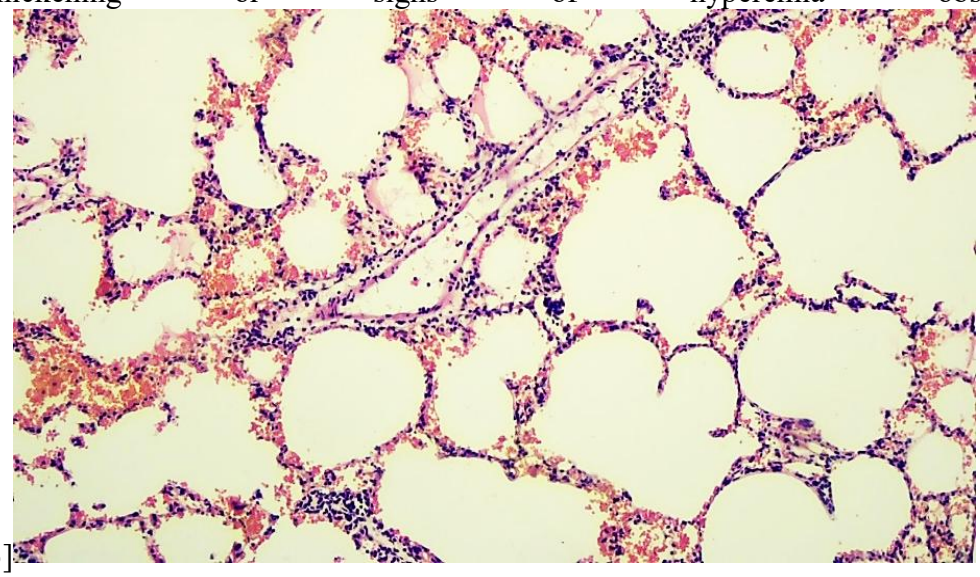


Fig. 3. Intact lung

In rats with alloxan-induced diabetes, fibrotic deposits were observed in the walls of pulmonary acini, along with significant narrowing of their lumens. Pulmonary blood vessels exhibited pronounced wall thickening and hyperemia. Lymphocytic infiltrates were noted around the vessels. Stain: H&E. Magnification ×200.

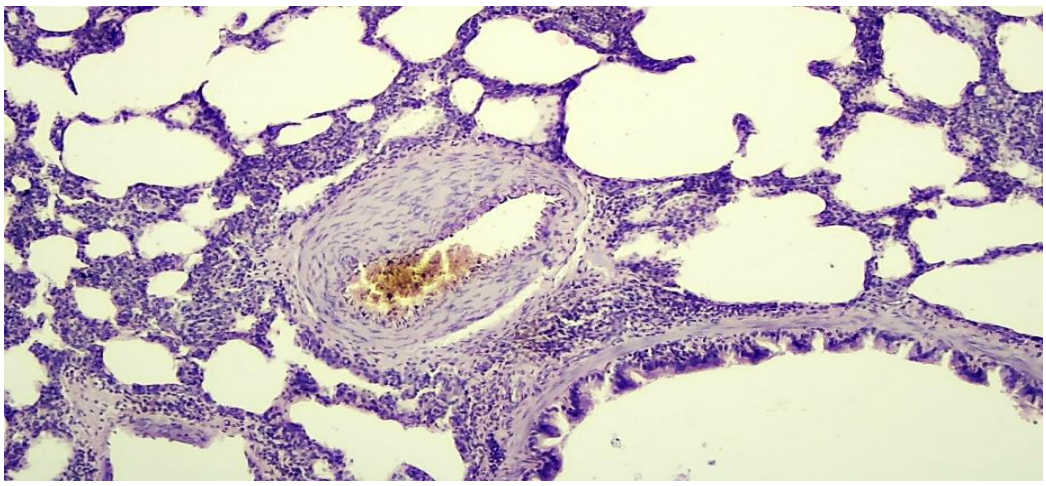


Fig. 4. Pulmonary blood vessels Lung parenchyma with focal lymphocytic accumulations and formation of lymphoid follicles. Stain: H&E. Magnification ×400.

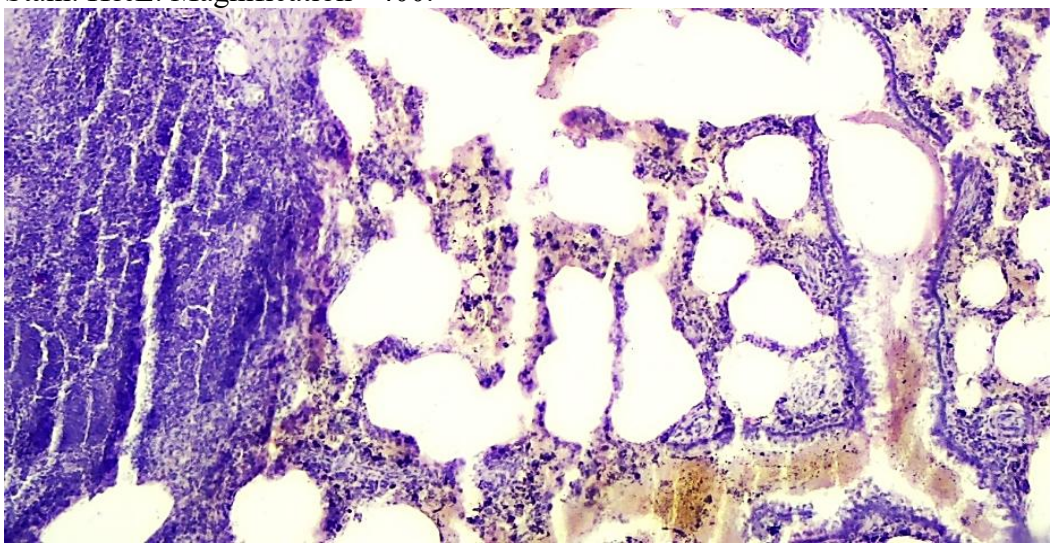


Fig. 5. Lung parenchyma

Conclusion: In rats with prolonged alloxan-induced diabetes, significant degenerative changes and signs of focal acinosis were observed, leading to impaired endocrine function of the pancreas. In the lung tissue of experimental animals, signs of fibrosis and lymphocytic infiltration were detected.

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