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HISTOLOGICAL CHANGES OF THE PANCREAS IN DIABETES MELLITUS

Kamoldinova Rokhatoy Abdullayevna
Lecturer, Andijan State Medical Institute (ASMI), Andijan, Uzbekistan
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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both. The pancreas plays a central role in the pathogenesis of diabetes because the endocrine islets of Langerhans contain β-cells responsible for insulin production. Diabetes mellitus is associated with characteristic structural and cellular alterations affecting both the endocrine and exocrine compartments of the pancreas. In type 1 diabetes mellitus, the major histological findings include immune-mediated destruction of pancreatic β-cells, reduction of β-cell mass, and insulitis. In type 2 diabetes mellitus, pancreatic changes are characterized by progressive β-cell dysfunction and loss, islet amyloid deposition, fibrosis, vascular alterations, and changes in the exocrine tissue. This thesis reviews the principal histological changes of the pancreas in diabetes mellitus and discusses their relationship with disease pathogenesis, progression, and impaired pancreatic function.

Keywords: diabetes mellitus, pancreas, histology, pancreatic islets, β-cells, insulitis, islet amyloid, pancreatic fibrosis, type 1 diabetes, type 2 diabetes.

INTRODUCTION

Diabetes mellitus is a group of chronic metabolic disorders characterized by persistent hyperglycemia caused by abnormalities in insulin secretion, insulin action, or a combination of both. The disease represents one of the most important endocrine disorders worldwide and is associated with progressive damage to multiple organs and tissues. Although the clinical manifestations of diabetes are primarily related to disturbances in glucose metabolism, the structural basis of the disease is closely connected with pathological changes occurring in the pancreas.The pancreas is a mixed endocrine and exocrine organ. Most pancreatic tissue consists of exocrine acinar cells and ductal structures that participate in the production and transport of digestive enzymes. The endocrine component is represented by the islets of Langerhans, which contain several hormonally active cell populations. β-cells produce insulin, α-cells secrete glucagon, δ-cells produce somatostatin, and pancreatic polypeptide cells contribute to regulation of digestive and metabolic functions. The coordinated activity of these endocrine cells is essential for maintaining normal glucose homeostasis.Under normal histological conditions, the islets of Langerhans appear as pale-staining clusters of endocrine cells distributed among darker-staining exocrine acini. The structural integrity and functional activity of pancreatic β-cells are particularly important for glucose regulation. Alterations in β-cell number, morphology, function, and interaction with surrounding cells therefore play a central role in the development of both type 1 and type 2 diabetes mellitus.

Type 1 diabetes mellitus is primarily an autoimmune disease characterized by immune-mediated destruction of insulin-producing β-cells. One of the characteristic histopathological findings is **insulitis**, an inflammatory infiltration of pancreatic islets mainly involving T lymphocytes and other immune cells. Progressive immune-mediated injury results in substantial reduction of β-cell mass and

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impairment of insulin production [1]. However, modern histopathological studies have demonstrated that β-cell destruction is heterogeneous and may not occur uniformly in all islets or in all patients. Residual insulin-containing β-cells can persist even after clinical diagnosis, particularly in individuals with later disease onset [1].In addition to β-cell loss, pancreatic tissue in type 1 diabetes may demonstrate increased expression of major histocompatibility complex molecules, inflammatory changes, extracellular matrix remodeling, cellular stress, and alterations in the microenvironment surrounding the pancreatic islets. These findings indicate that type 1 diabetes is not limited to simple disappearance of β-cells but involves a complex and prolonged pathological process affecting multiple components of pancreatic tissue [1].Histological abnormalities in type 1 diabetes are also observed in the exocrine pancreas. Studies have identified acinar atrophy, intralobular and interacinar fibrosis, leukocytic infiltration, fatty changes, and vascular abnormalities. Pancreatic volume may also be reduced in individuals with type 1 diabetes. These observations have increased interest in the functional relationship between the endocrine and exocrine compartments of the pancreas [2].

Type 2 diabetes mellitus has a different pathophysiological and histological pattern. The disease is characterized by insulin resistance combined with progressive β-cell dysfunction and an inability of pancreatic β-cells to maintain adequate insulin secretion. Over time, β-cell mass may decline as a result of cellular stress, apoptosis, metabolic overload, inflammation, and other pathological mechanisms.One of the most characteristic histological findings in type 2 diabetes is **islet amyloid deposition**. Pancreatic islet amyloid is largely composed of islet amyloid polypeptide, also known as amylin, which is normally produced and secreted together with insulin by β-cells. Under pathological conditions, human islet amyloid polypeptide can misfold and aggregate into oligomers and amyloid fibrils. Accumulation of these abnormal protein structures is associated with β-cell injury, decreased β-cell mass, and impaired insulin secretion [3].

Amyloid deposition may progressively disrupt the normal architecture of the islets of Langerhans. Histologically, amyloid appears as extracellular, eosinophilic, amorphous material within pancreatic islets and can be demonstrated more specifically using Congo red or other amyloid-sensitive staining techniques. Advanced islet amyloidosis may replace significant portions of endocrine tissue and contribute to progressive deterioration of β-cell function.Fibrotic changes are also important in diabetic pancreatic pathology. Recent histological studies have demonstrated increased pancreatic fibrosis in both type 1 and type 2 diabetes, although the distribution may differ. In type 1 diabetes, periductal and perivascular fibrosis appears more prominent, whereas type 2 diabetes may show greater lobular and parenchymal fibrosis. Type 2 diabetic pancreata have also demonstrated increased acinar-to-ductal metaplasia, angiopathy, and inflammatory-cell infiltration in the exocrine compartment [4].

These observations indicate that diabetes mellitus affects the pancreas as an integrated organ rather than exclusively affecting the endocrine islets. Endocrine dysfunction may influence exocrine tissue, while abnormalities in the exocrine microenvironment, pancreatic vasculature, extracellular matrix, and inflammatory pathways may in turn affect islet function.The histological differences between type 1 and type 2 diabetes are clinically important. In type 1 diabetes, the dominant pathological process involves autoimmune inflammation and β-cell destruction, whereas type 2 diabetes is characterized more prominently by β-cell dysfunction, progressive β-cell loss, amyloid deposition, metabolic stress, and structural remodeling. Despite these differences, both forms of diabetes ultimately involve deterioration of pancreatic endocrine function and structural abnormalities within pancreatic tissue.

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Histological assessment can provide valuable information about disease pathogenesis and progression. Conventional hematoxylin and eosin staining allows evaluation of general pancreatic architecture, while immunohistochemical staining for insulin, glucagon, CD3, CD8, and other cellular markers enables detailed assessment of endocrine-cell populations and inflammatory infiltration. Special stains such as Congo red can be used to demonstrate islet amyloid, while Masson's trichrome staining is useful for identifying and assessing pancreatic fibrosis.Understanding pancreatic histopathology is therefore important not only for describing tissue changes but also for explaining the mechanisms responsible for insulin deficiency and β-cell failure. Advances in immunohistochemistry, digital pathology, molecular imaging, and human pancreatic tissue repositories have significantly improved understanding of the structural changes occurring throughout the natural history of diabetes.The aim of this thesis is to analyze the major histological changes occurring in the pancreas in diabetes mellitus, with particular emphasis on β-cell loss, insulitis, islet amyloid deposition, fibrosis, vascular abnormalities, and alterations of the exocrine pancreas in type 1 and type 2 diabetes.

MAIN PART

Histological Structure of the Normal Pancreas

The normal pancreas consists of closely integrated exocrine and endocrine compartments. The exocrine component represents the major proportion of pancreatic tissue and is composed primarily of acinar cells arranged in clusters around a branching ductal system. Acinar cells contain abundant rough endoplasmic reticulum and apical zymogen granules responsible for the production and secretion of digestive enzymes. The endocrine component consists of the islets of Langerhans, which are scattered throughout the exocrine parenchyma and are highly vascularized.Within normal human pancreatic islets, β-cells constitute the predominant endocrine cell population and synthesize insulin. α-cells produce glucagon, δ-cells produce somatostatin, and smaller populations of pancreatic polypeptide and other endocrine cells are also present. The close anatomical relationship between endocrine cells, capillaries, extracellular matrix, and surrounding exocrine tissue is essential for normal pancreatic function.In routine hematoxylin and eosin staining, pancreatic islets appear as relatively pale cellular structures surrounded by darker exocrine acini. Immunohistochemical staining for insulin, glucagon, somatostatin, and other hormones allows individual endocrine-cell populations to be identified and quantified.

Histological Changes in Type 1 Diabetes Mellitus

Type 1 diabetes mellitus is characterized primarily by autoimmune destruction of insulin-producing pancreatic β-cells. Histologically, the two most characteristic abnormalities are reduction of β-cell mass and inflammatory infiltration of the pancreatic islets, known as insulitis [5].Insulitis is predominantly composed of lymphocytes. CD8-positive cytotoxic T lymphocytes represent an important component of the inflammatory infiltrate, although CD4-positive T cells, B lymphocytes, macrophages, and other immune cells may also be present. Immune cells are often located around or within insulin-containing islets and contribute to progressive β-cell injury.Importantly, insulitis is not uniformly distributed throughout the pancreas. Some islets may show considerable inflammation and β-cell loss, while other islets within the same pancreas may retain insulin-positive cells. This heterogeneous distribution indicates that autoimmune destruction is a dynamic process occurring at different stages in different islets [5].

Immunohistochemical staining for insulin demonstrates progressive reduction in insulin-containing β-cells. In advanced disease, some islets may become almost completely insulin-deficient while still containing glucagon-positive α-cells and other endocrine-cell populations. This selective

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destruction of β-cells is one of the characteristic pathological features of type 1 diabetes.The susceptibility of β-cells appears to be related not only to recognition by autoreactive immune cells but also to intrinsic biological differences between β-cells and other endocrine cells. β-cells may be more susceptible to endoplasmic reticulum stress, inflammatory cytokines, viral stress, and apoptosis than neighboring α-cells. Differences in anti-apoptotic mechanisms and immune-modulatory molecules may partly explain why α-cells usually survive despite being located within the same inflammatory environment [6].Another important finding in type 1 diabetes is increased expression of major histocompatibility complex class I molecules on pancreatic β-cells. Hyperexpression of HLA class I can increase the presentation of β-cell-derived antigens to cytotoxic T lymphocytes and may contribute to the maintenance of autoimmune β-cell injury.With progression of disease, islets may become smaller and contain markedly fewer β-cells. Nevertheless, complete disappearance of β-cells is not universal. Residual insulin-positive cells have been identified in some individuals even many years after the clinical diagnosis of type 1 diabetes. This observation suggests considerable heterogeneity in the rate and extent of β-cell destruction.

Exocrine Pancreatic Changes in Type 1 Diabetes

Type 1 diabetes is not restricted to the endocrine pancreas. Histological abnormalities have also been demonstrated in the exocrine compartment. These include acinar atrophy, fibrosis, vascular abnormalities, and inflammatory changes.A systematic histological analysis of human pancreatic tissue demonstrated increased acinar atrophy and angiopathy in pancreata from individuals with type 1 diabetes. Fibrosis was also increased, particularly around pancreatic ducts and blood vessels. Thus, periductal and perivascular fibrosis appears to be an important pattern of exocrine remodeling in type 1 diabetes [8].These changes may help explain the reduced pancreatic volume observed in many patients with long-standing type 1 diabetes. The relationship between endocrine β-cell destruction and exocrine pancreatic abnormalities remains incompletely understood, but reduced insulin trophic signaling, chronic inflammation, vascular abnormalities, and changes in pancreatic innervation may contribute.

Histological Changes in Type 2 Diabetes Mellitus

Type 2 diabetes mellitus has a different histopathological profile. Autoimmune insulitis is not the dominant lesion. Instead, the pancreatic islets demonstrate progressive β-cell dysfunction, variable reduction of β-cell mass, cellular stress, amyloid deposition, and structural remodeling.During the early stages of insulin resistance, pancreatic β-cells compensate by increasing insulin secretion. Prolonged metabolic demand eventually leads to progressive dysfunction. Chronic hyperglycemia, excessive exposure to fatty acids, oxidative stress, endoplasmic reticulum stress, inflammatory cytokines, mitochondrial dysfunction, and abnormal islet amyloid polypeptide accumulation have all been implicated in progressive β-cell failure [7].Histologically, the quantity of insulin-positive β-cells may become reduced. Increased β-cell apoptosis has been described, although functional impairment can occur before severe loss of β-cell mass. Therefore, the structural appearance of the pancreas does not always directly reflect the degree of functional insulin secretory failure.

Islet Amyloid Deposition

One of the most recognizable histological abnormalities associated with type 2 diabetes is amyloid deposition within the islets of Langerhans. The principal component of pancreatic islet amyloid is islet amyloid polypeptide, also known as amylin, which is normally synthesized and secreted together with insulin by β-cells.Under conditions of chronic β-cell stress, human islet amyloid polypeptide may misfold and aggregate into oligomers and fibrils. Amyloid accumulates extracellularly within pancreatic islets and may progressively alter normal islet architecture. Amyloid-associated cellular

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toxicity, oxidative stress, membrane disruption, and inflammatory mechanisms may further impair β-cell survival and function [7].In conventional histological sections, islet amyloid appears as homogeneous eosinophilic extracellular material. Congo red staining can be used for its identification, with amyloid demonstrating characteristic birefringence under polarized light. Thioflavin staining is another useful technique for identifying amyloid deposits.The severity of amyloid deposition varies considerably among individuals and between different islets in the same pancreas. Consequently, amyloid should be considered an important pathological feature of type 2 diabetes rather than the sole cause of β-cell failure.

Fibrosis and Exocrine Changes in Type 2 Diabetes

Fibrosis is increasingly recognized as an important component of pancreatic pathology in type 2 diabetes. Histological studies demonstrate increased collagen deposition within the pancreatic parenchyma. Compared with type 1 diabetes, fibrosis in type 2 diabetes tends to show a more lobular and intraparenchymal distribution [8].A 2024 systematic histological analysis of human pancreatic tissue showed that pancreata from individuals with type 2 diabetes had increased acinar-to-ductal metaplasia, angiopathy, and lobular fibrosis compared with matched individuals without diabetes. Quantitative Masson's trichrome analysis demonstrated a larger proportion of fibrotic pancreatic tissue in type 2 diabetes [8].Acinar-to-ductal metaplasia is characterized by replacement or transformation of normal acinar structures into duct-like epithelial structures. Its increased frequency suggests that chronic metabolic injury affects the exocrine pancreas as well as the endocrine islets.Vascular abnormalities are another component of diabetic pancreatic pathology. Thickening and remodeling of small vessels may compromise pancreatic microcirculation, potentially contributing to tissue hypoxia, fibrosis, and impaired endocrine and exocrine function.

Table 1. Comparison of Major Histological Changes in Type 1 and Type 2 Diabetes Mellitus

Histological feature	Type 1 diabetes mellitus	Type 2 diabetes mellitus
β-cell mass	Markedly reduced due to autoimmune destruction	Variable but generally progressively reduced
Insulin-positive cells	Markedly decreased; residual cells may persist	Reduced or functionally impaired
Insulitis	Characteristic, especially near disease onset	Not a classical dominant feature
Main inflammatory cells	Predominantly T lymphocytes, particularly CD8+ cells	Low-grade inflammatory changes may occur
α-cells	Generally preserved compared with β-cells	Usually relatively preserved
HLA class I expression	Frequently increased in insulin-containing islets	Not a characteristic primary finding
Islet amyloid	Usually absent	Common and characteristic
β-cell apoptosis	Immune-mediated and stress-associated	Metabolic stress and amyloid-associated mechanisms
Acinar atrophy	Increased	May occur but less characteristic

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Histological feature	Type 1 diabetes mellitus	Type 2 diabetes mellitus
Acinar-to-ductal metaplasia	Less prominent	Increased
Fibrosis	Predominantly periductal and perivascular	More lobular and parenchymal
Angiopathy	Increased	Increased
Main pathological mechanism	Autoimmune β-cell destruction	Insulin resistance with progressive β-cell dysfunction
Important histological stains	H&E, insulin IHC, CD3/CD8, HLA-I	H&E, insulin IHC, Congo red, thioflavin, Masson's trichrome

Histological and Immunohistochemical Methods

Histopathological evaluation of the diabetic pancreas requires a combination of conventional staining, special staining, and immunohistochemical techniques. Hematoxylin and eosin staining remains the basic method for assessing overall pancreatic architecture, acinar morphology, islet structure, inflammation, vascular abnormalities, and other morphological changes.

Immunohistochemistry for insulin is essential for identifying β-cells and evaluating the proportion of insulin-containing endocrine tissue. Glucagon staining can be used to identify α-cells and demonstrate their relative preservation, particularly in type 1 diabetes.CD3 and CD8 immunostaining are useful for demonstrating T-lymphocyte infiltration and evaluating insulitis. Additional staining for CD20 can identify B lymphocytes, while macrophage markers may be used to assess innate immune-cell infiltration. In type 1 diabetes, staining for HLA class I molecules can demonstrate abnormal hyperexpression in affected islets [5, 6].Congo red and thioflavin staining are particularly useful in type 2 diabetes because they demonstrate islet amyloid deposits. Immunohistochemistry directed against islet amyloid polypeptide can further characterize the composition of these deposits.

Masson's trichrome is widely used for evaluation of collagen deposition and pancreatic fibrosis. It allows fibrotic connective tissue to be distinguished from normal pancreatic parenchyma and enables quantitative or semiquantitative comparison of fibrosis between diabetic and non-diabetic pancreatic specimens [8].Apoptotic cells can be investigated using techniques such as TUNEL staining and activated caspase markers. Modern studies increasingly use multiplex immunofluorescence, digital pathology, whole-slide imaging, and automated image analysis to quantify multiple cellular populations simultaneously. These methods provide detailed spatial information regarding the relationship between β-cells, immune cells, blood vessels, extracellular matrix, and exocrine structures.

Histopathological Significance

The histological findings demonstrate that diabetes mellitus produces extensive structural changes throughout the pancreas. In type 1 diabetes, autoimmune inflammation and selective destruction of β-cells represent the dominant pathological process. In type 2 diabetes, β-cell dysfunction and progressive loss occur in association with metabolic stress, amyloid accumulation, fibrosis, and structural remodeling.The identification of distinct fibrosis patterns in type 1 and type 2 diabetes further supports the concept that the two disorders affect pancreatic tissue through different mechanisms. Type 1 diabetes demonstrates more prominent periductal and perivascular fibrosis, while type 2 diabetes is associated with greater intralobular and parenchymal fibrosis [8].Importantly, pancreatic pathology is heterogeneous. Not all islets within the same pancreas show identical changes,

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and the severity of β-cell loss, inflammation, amyloid deposition, or fibrosis can vary according to disease duration, age at onset, metabolic status, and individual biological characteristics.Therefore, modern histological evaluation should combine morphological findings with immunohistochemical and molecular markers. A comprehensive assessment of both endocrine and exocrine compartments provides a more complete understanding of the pathogenesis and progression of diabetes mellitus.

CONCLUSION

Diabetes mellitus is associated with significant histological changes in both the endocrine and exocrine compartments of the pancreas. Although type 1 and type 2 diabetes mellitus differ in their primary pathogenic mechanisms, both conditions ultimately lead to structural damage of pancreatic tissue and progressive impairment of β-cell function.In type 1 diabetes mellitus, the most characteristic histological findings are autoimmune insulitis, selective destruction of insulin-producing β-cells, reduction of β-cell mass, and persistence of inflammatory changes within and around the pancreatic islets. Exocrine abnormalities, including acinar atrophy, fibrosis, and vascular changes, may also develop and demonstrate that the pathological process is not limited to the endocrine pancreas.In type 2 diabetes mellitus, the dominant changes include progressive β-cell dysfunction and loss, islet amyloid deposition, fibrosis, vascular remodeling, and structural alterations of the exocrine pancreas. Amyloid accumulation and chronic metabolic stress contribute to deterioration of islet architecture and impaired insulin secretion. Increased acinar-to-ductal metaplasia and lobular fibrosis further indicate that type 2 diabetes affects the pancreas as an integrated organ.Histological and immunohistochemical methods are essential for identifying these pathological changes. Hematoxylin and eosin staining provides general morphological assessment, whereas insulin, glucagon, CD3, CD8, and HLA class I immunostaining can demonstrate endocrine-cell changes and immune infiltration. Congo red staining is useful for detecting islet amyloid, while Masson's trichrome allows assessment of pancreatic fibrosis.In conclusion, histological examination of the pancreas provides important information about the mechanisms and progression of diabetes mellitus. Better understanding of β-cell loss, inflammation, amyloid deposition, fibrosis, and exocrine remodeling may contribute to improved interpretation of disease pathogenesis and may support the development of future therapeutic strategies aimed at preserving pancreatic structure and function.

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