Volume 2, Issue 5, May 2024 ISSN (E): 2938-3765

# MORPHOLOGICAL AND MORPHOMETRIC CHANGES OBSERVED IN THE THYMUS IN DIABETIC PATIENTS

Nazarov. B. S.
Assistant Teacher of Tashkent Medical Academy,
Department of Histology and Medical biology
E-mail:info@tma.uz

Abdijamilova Z. A.
Student,Tashkent Medical Academy
E-mail:abdijamilovazerzada6@gmail.com

**Abstract**

When you consume some food item that contains carbohydrates, your body turns it into glucose and takes help from Insulin to transport it to different tissues through the bloodstream. Insulin is one of the hormones that the pancreas produces. In most cases, diabetes mellitus can result in devastating complications if left untreated. For almost all types of this disease, insulin is recommended. Diabetes is due to either t he pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus:

• Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown

• Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.

• Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level.This is because when you have diabetes, your body stops making or using enough Insulin to manage the glucose level. As a result, blood glucose starts accumulating and causes severe effects like kidney failure, eye or ear infections, etc.

**Keywords**: Type1, Type 2, Type 3, Diabetes Mellitus, T cell, thymocytes, epithelial cells, hyperglycemia.

## Introduction

Diabetes mellitus, commonly referred to as diabetes, is a chronic metabolic disorder characterized by high blood sugar levels over a prolonged period. It affects millions of people worldwide and poses significant health challenges. Among the various complications associated with diabetes,



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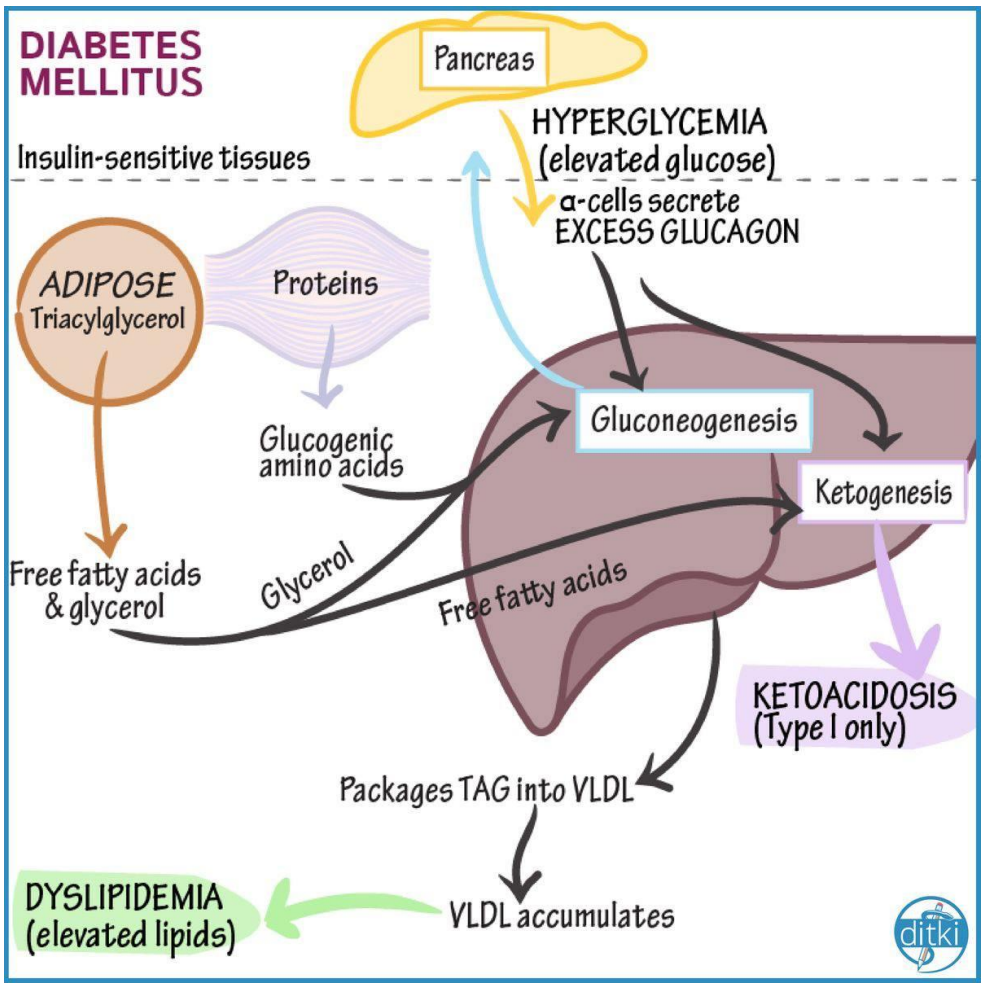
alterations in organ morphology and function are frequently observed. One such organ that undergoes changes in diabetic individuals is the thymus, a crucial component of the immune system responsible for T-cell maturation and regulation.

**MATERIALS AND METHODS:**




**Thymus Function and Structure:**

The thymus is a specialized primary lymphoid organ located in the upper chest, behind the sternum. It plays a vital role in the development and maturation of T lymphocytes or T cells, which are essential for adaptive immunity. During early life, the thymus is particularly active, producing and educating T cells to recognize and respond to foreign pathogens while tolerating self-antigens.

**The pivotal role of thymus in T1DM**

T1DM is predominantly a complex T cell-mediated autoimmune disease in which the pancreatic insulin-producing β-cells are selectively destroyed by the immune system. As a result, the generation of insulin declines significantly, resulting in a relative or absolute deficiency of insulin. The causes of this destructive process are still not well understood but a combination of genetic susceptibility and environmental triggers such as viral infection, toxins, and some dietary factors have been suggested. The disease can develop at any age but T1DM occurs most frequently in children and adolescents.



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With the deepening of studies, researchers have found that T1DM is not only related to autoimmunity, but also associated with inflammation Although the role of certain cytokines in the pathogenesis of T1DM is still somewhat under debate, it is clear that these cytokines are indeed involved in the process. Currently, *T*-cell transfer model of T1DM has been used in many models of T1DM. Data from the *T*-cell transfer model suggested that IFN-γ may be an important *T*-cell-derived cytokine in the pathogenesis of T1DM. CD4 + T cells can differentiate into several different effector subgroups, the best features are Th1, Th2 and Th17 cells. And *T*-bet, the Th1 master transcription factor, is essential for the development of T1DM because its absence leads to diabetic resistance. It has been shown that populations from Th1 and Th17 cells can mediate the transfer of T1DM to the lymphopenic receptors, however, Th17 is due to the conversion to a Th1-like phenotype. The study by Cooke et al. showed that IFNγ derived from effector T cells can upregulate the expression of inducible nitric oxide (iNOS) in the pancreas and also enhance the expression of MHC class II on pancreatic infiltrating CD11b + cells. The research of Martin-Orozco et al. proved that Th17 cells promote pancreatic inflammation. In spontaneous animal models, all mouse infiltrates contain a high proportion of Treg, which indicates that there are active attempts to regulate inflammation.

The expression of insulin-related peptides in the thymus was hypothesized as early as 1965. Pansky et al. reported the presence of insulin-like peptides in the thymus of AKR mice, as well as in bovine and porcine species, based on the presence of diseases such as hypoglycemia and thymic hyperplasia associated with lymphoid leukemia in female AKR mice. Subsequent studies have shown that several neuroendocrine-related genes were transcribed in TECs of animals and humans such as insulin-like growth factor 2(IGF-2) which is a member of the insulin family and mainly expressed in rodent and human TECs. Autoimmune regulatory protein (AIRE), which is a downstream gene of FoxN1, regulates the transcription of most neuroendocrine-related genes in TEC. Depending on their genetic background, AIRE−/− mice exhibit several signs of peripheral autoimmunity, which are associated with a significant decrease in thymic transcription of neuroendocrine genes (such as IGF-2)

**The pivotal role of thymus in T2DM**

There is increasing evidence linking low-grade chronic inflammation and immune cells to the occurrence of T2DM and related complications. Chronic low-grade inflammation and impaired insulin sensivity_has been associated with fewer Tregs in adipose tissue, and reversal of insulin sensivity_following Tregs restoration has been demonstrated. T cells can secrete or promote the secretion of a variety of inflammatory factors, thereby participating in various immune responses and inflammatory reactions.

IL-10 has been shown to improve impaired insulin signaling caused by pro-inflammatory cytokines.. When administered in vivo, IL-10 prevents the development of IL-6 or lipid-induced insulin resistance. In addition, IL-10 inhibits NADPH oxidase and suppresses oxidative stress, thereby blocking insulin metabolic signaling. These results imply that IL-10 plays an important role in modulation of cardiovascular insulin resistance. IL-6, considered as a pro-inflammatory cytokine and a predictor of T2DM, was originally considered to mediate adverse metabolic effects, contributing to insulin resistance and deteriorating glucose homeostasis. But the role of IL-6 in insulin resistance still remains controversial.



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TNF-α, a pro-inflammatory cytokine, can affect peripheral insulin resistance and insulin secretion. The expression of TNF-α in adipose tissue was increased. Furthermore, it stimulated the expression of resistin in human macrophages and inhibited the expression of adiponectin in human adipocytes in patients with metabolic diseases: such as T2DM

**Morphological Changes in Diabetic Thymus:**

In diabetic individuals, the thymus undergoes various morphological alterations, which can have implications for immune function. Studies have reported structural changes such as reduced thymic size, altered architecture, and changes in cell composition. These changes may result from the direct effects of hyperglycemia, as well as secondary complications associated with diabetes, including oxidative stress and inflammation.

**Aging in Thymus:**

DM is an age-related disease, the incidence of which increases as age grows. DM is also associated with chronic low-level inflammatory activity and can be triggered or worsened by systemic inflammation. Moreover, chronic systemic inflammation has been found to be related to all-cause mortality risk in elderly adults.

Thymus is an aging organ. But there are evidences that the processes of positive and negative selection appear to remain qualitatively intact, despite the reduced number of cortical and medullary thymocytes in the aged thymus. Moreover, animal studies found that the naive T cells produced by thymus remained normal function although aged thymus had a lower productivity in mice. Increasing the input of functional thymus progenitor cells can trigger an expansion of TECs, which in turn create new niches for *T*-cell lineage commitment and facilitate the proliferation of thymocyte. Alternatively, the decline of these factors caused by aging may trigger a downward spiral and cause further deterioration of thymus function and systemic inflammation.

Aging reduces immune function partly due to a reduction in production of naïve T cells induced by thymus involution.Thymus transcription factors forkhead box N1 is the most important factor to maintain complete thymus physiological function. Previous studies have found that the expression of FoxN1 was down-regulated as age grew, yet increased FoxN1 expression can improve thymus function and even promote thymus regeneration. It has determined that FoxN1 regulates the expression of genes involved in antigen processing and thymocyte selection, in addition to the transcriptional control of genes involved in the attraction and lineage commitment of T cell precursors. Therefore, there are reasons to believe that the thymus FoxN1 may be involved in the process of DM.

**Reduced Thymic Size:**

One of the most commonly observed morphological changes in the thymus of diabetic patients is a decrease in size. Histological examinations often reveal thymic atrophy, characterized by a reduction in both the overall size of the organ and the number of thymocytes present. This reduction in thymic volume may impair the production and selection of T cells, leading to compromised immune responses.

**Altered Thymic Architecture:**



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In addition to changes in size, diabetic thymi may exhibit alterations in their architectural organization. These alterations can include disruptions in the thymic epithelial network, changes in the distribution of cortical and medullary regions, and alterations in the organization of thymic stromal cells. Such architectural changes may impact the efficiency of T cell development and selection within the thymus.

**Changes in Cell Composition:**

The cellular composition of the thymus is also affected in diabetic individuals. Studies have shown alterations in the relative abundance of different thymic cell populations, including thymocytes, thymic epithelial cells, and dendritic cells. These changes may result from dysregulated thymic homeostasis and impaired cell differentiation processes, ultimately influencing the generation of mature and functional T cells.

**Morphometric Analysis of Diabetic Thymus:**

In addition to qualitative assessments of thymic morphology, morphometric analyses provide quantitative insights into structural changes in the diabetic thymus. Techniques such as stereology, histomorphometry, and imaging analysis allow for the measurement of various parameters, including thymic volume, cellularity, and spatial organization. These analyses help to characterize the extent and nature of thymic alterations in diabetes and provide valuable data for understanding disease pathogenesis.

**CONCLUSION**:

In conclusion, diabetic individuals frequently exhibit morphological and morphometric changes in the thymus, a key organ involved in immune function. These changes, including thymic atrophy, alterations in architecture, and changes in cell composition, can have significant implications for immune homeostasis and host defense mechanisms. Further research is needed to elucidate the underlying mechanisms driving thymic alterations in diabetes and to explore potential therapeutic interventions aimed at preserving thymic function in affected individuals. By understanding the relationship between diabetes and thymic morphology, we can gain insights into novel strategies for managing immune dysfunction and improving health outcomes in diabetic patients.

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