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Role of Adenosine Deaminase in the Pathophysiology of Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) represents the most prevalent metabolic disorder worldwide and is characterized by persistent hyperglycemia resulting from insulin resistance and relative insulin deficiency. Chronic elevation of blood glucose promotes oxidative stress and immune dysregulation, contributing to progressive damage of vital organs such as the kidneys, nerves, eyes, and cardiovascular system. Adenosine deaminase (ADA), a key enzyme in purine metabolism, plays an essential role in regulating adenosine concentration and immune cell activity. Increased ADA activity, particularly its ADA2 isoform, has been consistently observed in individuals with T2DM and is closely associated with impaired insulin action, enhanced lipolysis, and inflammatory responses. This review critically examines the pathophysiology of T2DM, outlines the biological functions of ADA and its isoenzymes, and highlights current evidence linking elevated ADA activity with glycemic dysregulation and diabetic complications.

Keywords:- Type 2 diabetes mellitus, Adenosine deaminase, Insulin resistance, Hyperglycemia

1. INTODUCTION

Diabetes mellitus comprises a group of chronic metabolic disorders defined by sustained hyperglycemia. Among its subtypes, type 2 diabetes mellitus (T2DM) accounts for the majority of cases and poses a major global public health burden. The disorder arises from a complex interaction between genetic susceptibility and environmental influences such as sedentary lifestyle, unhealthy dietary habits, obesity, and aging. Persistent hyperglycemia in T2DM initiates a cascade of metabolic and vascular abnormalities that ultimately lead to long-term complications and reduced quality of life.

In addition to impaired glucose metabolism, T2DM is associated with chronic low-grade inflammation, oxidative stress, and dysregulation of immune responses, all of which play critical roles in disease progression. These pathological alterations contribute to endothelial dysfunction, altered lipid metabolism, and progressive β-cell failure, thereby exacerbating insulin resistance and glycemic instability. Furthermore, prolonged metabolic imbalance increases the risk of microvascular complications such as nephropathy, neuropathy, and retinopathy, as well as macrovascular conditions including cardiovascular and cerebrovascular diseases.

Recent research has emphasized the importance of biochemical markers involved in inflammatory and metabolic pathways to better understand the underlying mechanisms of T2DM. Among these, adenosine deaminase (ADA), an enzyme involved in purine metabolism and immune regulation, has gained significant attention due to its altered activity in diabetic conditions. Elevated ADA levels have been reported in patients with T2DM and are believed to influence insulin sensitivity, lipid metabolism, and inflammatory processes. Therefore, exploring the role of ADA in the pathophysiology of T2DM may provide valuable insights into disease mechanisms and support the development of improved diagnostic and prognostic strategies.

The pathogenesis of T2DM is primarily driven by insulin resistance in peripheral tissues, including skeletal muscle, liver, and adipose tissue, accompanied by inadequate compensatory insulin secretion by pancreatic β-cells. Elevated circulating free fatty acids, chronic inflammation, and oxidative stress further impair insulin signaling pathways, exacerbating glucose intolerance. Over time, β-cell dysfunction progresses, resulting in worsening hyperglycemia and metabolic instability.

At the molecular level, defects in insulin receptor signaling and post-receptor pathways reduce glucose uptake in skeletal muscle and promote excessive hepatic glucose production. Adipose tissue dysfunction contributes to increased release of pro-inflammatory cytokines and adipokines, such as tumor necrosis factor-α and interleukin-6, which further interfere with insulin action. These inflammatory mediators activate stress-sensitive signaling cascades, intensifying insulin resistance and metabolic imbalance.

Oxidative stress plays a crucial role in the progression of T2DM by damaging cellular macromolecules and impairing mitochondrial function. Persistent hyperglycemia enhances the production of reactive oxygen species, leading to endothelial dysfunction and altered cellular metabolism. In addition, glucotoxicity and lipotoxicity

exert toxic effects on pancreatic β-cells, reducing insulin biosynthesis and secretion capacity. The combined effects of insulin resistance, β-cell failure, inflammation, and oxidative stress establish a self-perpetuating cycle that accelerates disease progression and increases susceptibility to chronic diabetic complications.

2.ADENOSINE DEAMINASE: BIOLOGICAL ROLE AND ISOENZYMES

Adenosine deaminase (ADA; EC 3.5.4.4) is a critical enzyme involved in purine metabolism, catalyzing the irreversible deamination of adenosine to inosine. ADA activity is widely distributed across human tissues, with particularly high expression in lymphoid organs, reflecting its essential role in immune system development and function. By regulating extracellular and intracellular adenosine concentrations, ADA influences a wide range of physiological processes, including cellular proliferation, differentiation, and immune modulation.

Two principal isoenzymes have been identified: ADA1, which is ubiquitously expressed and essential for lymphocyte viability, and ADA2, which is predominantly derived from monocytes and macrophages and exhibits cytokine-like properties. ADA1 is primarily involved in intracellular adenosine metabolism and is crucial for maintaining normal immune cell function, whereas ADA2 is secreted into the extracellular environment and participates in inflammatory signaling pathways. Alterations in ADA2 activity have been linked to immune activation, endothelial dysfunction, and chronic inflammatory states.

Beyond its immunological role, ADA has been implicated in metabolic regulation through its effects on insulin sensitivity and glucose homeostasis. Elevated ADA activity reduces adenosine availability, thereby diminishing its insulin-sensitizing and anti-inflammatory effects. This imbalance may promote increased lipolysis, oxidative stress, and inflammatory responses, particularly in metabolic disorders such as type 2 diabetes mellitus. Consequently, ADA has emerged as a potential biochemical marker reflecting both immune and metabolic dysregulation, highlighting its clinical relevance in chronic metabolic diseases.

3.RELATIONAL BETWEEN ADA ACTIVITY AND T2DM

Accumulating evidence indicates that serum ADA activity is significantly elevated in patients with T2DM compared with healthy individuals. Increased ADA activity reduces extracellular adenosine levels, thereby attenuating insulin-mediated glucose uptake and promoting lipolysis through cyclic AMP–dependent pathways. The resulting rise in free fatty acids and reactive oxygen species contributes to insulin resistance and inflammatory damage. Several clinical studies have proposed ADA, particularly the ADA2 isoenzyme, as a potential biochemical marker for glycemic control and disease progression in T2DM.

Moreover, elevated ADA activity has been correlated with poor glycemic indices, including increased fasting plasma glucose and glycated hemoglobin levels, suggesting a direct association between ADA and metabolic control. The reduction in adenosine-mediated vasodilation and anti-inflammatory effects further exacerbates endothelial dysfunction, a key contributor to diabetic microvascular and macrovascular complications. ADA-driven immune activation may also enhance the production of pro-inflammatory cytokines, creating a sustained inflammatory environment that accelerates disease progression.

Recent findings suggest that ADA2 plays a dominant role in linking immune dysregulation with metabolic impairment in T2DM. As ADA2 is primarily secreted by activated monocytes and macrophages, its increased activity reflects underlying immune activation associated with chronic hyperglycemia. Consequently, monitoring ADA activity may not only aid in assessing glycemic status but also provide insight into inflammatory burden and risk stratification for diabetic complications, supporting its potential utility as a complementary biomarker in clinical practice.

4.DIABETIC COMPLICATIONS

Prolonged hyperglycemia in T2DM is associated with both microvascular and macrovascular complications. Microvascular damage manifests as diabetic nephropathy, neuropathy, and retinopathy, while macrovascular complications include coronary artery disease and cerebrovascular events. Oxidative stress, endothelial dysfunction, and immune activation play central roles in the development of these complications.

Chronic exposure to elevated glucose levels leads to the formation of advanced glycation end products, activation of the polyol pathway, and increased protein kinase C activity, all of which contribute to vascular injury and tissue damage. These biochemical alterations disrupt normal cellular signaling and compromise vascular integrity, thereby accelerating the progression of diabetic complications. Additionally, persistent inflammation and oxidative stress impair nitric oxide bioavailability, further promoting endothelial dysfunction and atherosclerotic changes.

The severity and progression of diabetic complications are closely influenced by the duration of diabetes, degree of glycemic control, and presence of associated metabolic abnormalities such as dyslipidemia and hypertension. Early identification of risk factors and timely intervention are essential to reduce morbidity and improve long-term outcomes in patients with T2DM. Understanding the underlying mechanisms of these complications may

also facilitate the development of targeted therapeutic strategies aimed at preventing disease progression and improving quality of life.

5. CONCLUSION

The available literature strongly supports a close association between increased ADA activity and the pathophysiological mechanisms underlying T2DM. Elevated ADA levels contribute to impaired insulin action, enhanced lipolysis, oxidative stress, and immune dysregulation, thereby accelerating disease progression and the development of diabetic complications. These multifactorial effects highlight the significant role of ADA in linking metabolic dysfunction with inflammatory processes in T2DM.

Monitoring ADA activity may offer additional insight into metabolic control and risk stratification in patients with T2DM, particularly when used alongside conventional glycemic markers. Furthermore, ADA, especially the ADA2 isoenzyme, may serve as a valuable adjunct biomarker reflecting both immune activation and metabolic imbalance. Future research focusing on large-scale clinical studies and therapeutic modulation of ADA activity may further clarify its potential role in improving disease management and preventing long-term complications associated with type 2 diabetes mellitus.

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