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Conceptual Paper

Adenosine Deaminase and its Role in Diabetes Mellitus Type 2: Possible Marker of Insulin Resistance?

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Adenosine deaminase (ADA) is a ubiquitously expressed enzyme, found in the cytosol where it catalyzes the irreversibly deamination of adenosine (deoxyadenosine) into inosine (deoxyinosine), in the purine pathway. ADA expression and activity is vital for the metabolism of purines, regulating the concentration of adenosine through the deamination process [1,2]. Absent or deficient ADA activity leads to the accumulation of the enzyme substrates, such as deoxyadenosine, which is a toxic metabolite related to the inhibition of DNA synthesis [3].

It is well known that ADA plays a pivotal role in the differentiation and proliferation of lymphocytes and monocytes, being used in the monitoring of diseases of the immune system [4]. Moreover, the genetic deficiency of ADA leads to severe combined immunodeficiency disease [5], while elevated levels of the enzyme have been linked to the proliferation and activation of inflammatory cells [6,7]. High lymphocytic ADA activities have been reported in diseases associated with altered cell-mediated immune responses, such as leukemia and tuberculosis [8-11]. Therefore, it is considered a good marker of cell-mediated immune response.

Diabetes mellitus (DM) is a multifactorial metabolic disorder characterized by the phenotype of hyperglycemia. While diabetes mellitus type 1 (T1DM) is an autoimmune disease that affects insulin production by pancreatic β-cell, the hyperglycemia found in diabetes mellitus type 2 (T2DM) is due to a progressive failure of pancreatic β-cell insulin secretion followed by insulin resistance [12]. The International Diabetes Federation (IDF) estimated in 2019 that almost 463 million adults were affected by DM and the projection to 2045 is that 700 million will suffer from the disease [13]. The link between ADA and DM has become more evident, since some studies have reported that ADA is positively correlated with HbA1c which is the hallmark of metabolic control [14-16]. Increased ADA activity is also implicated in the increased inflammatory state of a cell; therefore ADA is considered a marker of inflammation and the immunological status [17]. Patients with DM frequently show decreased cell mediated immunity probably due to loss of metabolic control which can lead to inappropriate lymphocyte function. Moreover, insulin regulates T lymphocyte metabolism supporting adequate energy for lymphocyte function, differentiation and proliferation [18,19]. Thus, defects in insulin action, found in T2DM, might decrease T-lymphocyte function. Indeed, severe hyperglycemia reduces the function of immune cells and increases inflammation [20].

It has been shown that ADA activity is increased in metabolic disease such as T2DM and metabolic syndrome [21,22]. The increase in ADA activity found in T2DM may reflect alteration in insulin action, as insulin seems to modulate the activity of ADA in T2DM patients, suggesting a positive correlation between ADA levels and insulin [23]. Besides, adenosine increases glucose uptake, thus in T2DM the increased ADA levels, will decrease adenosine levels, favoring insulin resistance. It was suggested that the suppression of ADA activity would ameliorate insulin sensitivity and lymphocytes' inflammatory state, both related to the pathogenesis of T2DM. Moreover, it has been suggested that ADA may also modulate the bioactivity of insulin [24], but its clinical significance in DM needs more investigations.

Conclusion

The increased ADA activity found in T2DM patients may indicate a poor glycemic control, as adenosine, the enzyme substrate, decreases. This argument is supported by the fact that ADA is positively correlated with HbA1c. There are few works considering pre-diabetics groups and ADA would be a good marker of the progression of the pre-diabetic state to T2DM, as inflammation and decreased immune response are involved in the pathogenesis of the disease. However, there are no conclusive data showing that changes in ADA activity will result in insulin resistance.

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