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Adenosine deaminase activity in type 2 diabetes mellitus

Chronic hyperglycaemia is associated with oxidative stress and chronic low grade inflammation which is said to play a vital role in the pathogenesis of type 2 diabetes mellitus (T2DM),[1] which is a forerunner of cardiovascular disease (CVD). Oxidative stress leads to oxidative damage to lipids in a process of lipid peroxidation, which is assessed by an increase in levels of the malondialdehyde (MDA) a marker of lipid peroxidation.[2] Oxidative stress is reported to be present even in newly diagnosed T2DM.[2,3]Adenosine deaminase (ADA), an enzyme of purine metabolism which by a process of deamination converts purine nucleoside adenosine to ionosine in virtually all the cells. Adenosine is found to exert an anti-inflammatory effect and, therefore, ADA may regulate the inflammatory response.[4]

ADA activity has been reported to be elevated in the serum of patients with T2DM.[3,5] Hence the present study was taken up with the primary objective of assessing serum ADA levels in T2DM and secondary objective being to study the associations of ADA with oxidative stress and fasting blood sugar levels. Thirty subjects with T2DM (16 males, mean age 56.4±6.3 years) diagnosed as per American Diabetes Association criteria,[6] attending Endocrinology outpatient department at Sri Venkateswara Institute of Medical Sciences, who were treatment naive were included as cases.

Thirty subjects without T2DM (18 males, mean age 52.6±8.2 years) were included as controls. Informed consent was obtained from all the participants. Subjects with active infection, smokers and alcohol users were excluded from the study. The study was approved by the Institutional Ethics Committee.

Five mL of peripheral venous blood sample were collected from subjects who were fasting for 8-12 hrs. Three mL of blood was transferred into additive free plain bottles and two mL was transferred into sodium fluoride and potassium oxalate anticoagulant containing bottles. The plain samples were allowed to stand for half an hour, and centrifuged at 3000 rpm for 15 minutes and the serum obtained was stored at –80 ^{o}C until analysis. The sample from anticoagulant bottle was centrifuged immediately and the plasma was analyzed for glucose on the same day. Glucose assay was performed by glucose oxidase peroxidase method using commercial kit from Aspen Laboratories Pvt. Ltd., Delhi, India. Estimation of serum ADA was done by spectrophotometric method of Galanti and Giusti using a commercial kit obtained from Microxpress ADA-MTB Tulip diagnostics Pvt Ltd, India on ultraviolet-visual (UV/VIS) spectrophotometer. Serum MDA was measured as thiobarbituric reactive substances (TBARS) on UV/VIS spectrophotometer.[7]

The data distribution was tested using Kolmogorov-Smirnov test. Differences between the means for the variables between groups were analyzed using Mann-Whitney U test. Spearman rank correlation was used to test

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the correlations among the variables. A p-value of < 0.05 was considered statistically significant. The statistical analysis was performed using statistical software, SPSS version 16 (SPSS, Inc., Chicago IL).

We have observed an elevation in serum ADA activity in T2DM (Table 1). We also observed a significant positive correlation between serum ADA levels, (MDA) (r=0.647; p<0.001); FBG (r=0.681; p<0.001). Significant positive correlation with fasting blood sugar and MDA levels. These are in agreement with similar studies which have observed changes in ADA activity.[8,9] The chronic inflammatory state of T2DM induces destruction of pancreatic β-cells, causing release of β-cell antigens. When T-cells encounter these antigens, they get activated and mount an immune response leading to further destruction of the β-cells. Therefore inflammation generates an immune response and is also hypothesized to be one of the factors promoting oxidative stress.[10] High amounts of glucose is chiefly responsible for initiating oxidative stress in the islet cells of the pancreas.[11] Purine metabolism is also associated with generation of superoxide, formed as a byproduct part of the reactions catalyzed by zanthine oxidase. Hence increase in purine metabolism is associated with a concomitant increase in free radical generation. ADA is hence related to the production of free radicals and oxidative stress. A possible relation of microvascular complications of diabetes mellitus and ADA activity has been hypothesized.[3]

Pharmacological agents have also been found to regulate ADA activity, the downregulation of which was observed to reduce MDA production.[12] It was observed that treatment of T2DM in animal models with Roglitazone was found to prevent increased levels of lipid hydroperoxide and metformin or troglitazone, which were reported to possess antioxidant properties, were found to prevent hyperglycaemia in these models.[10,11] It has been reported that treatment with metformin showed a significant decrease in ADA activity when compared to sulfonylurea treated group.[9] Similarly statins have also found to reduce ADA activity which may be due to the other effects of statins such as anti-inflammatory actions, inhibition of T-cell differentiation, inhibition of tumour necrosis factor (TNF-α) , and other immune regulatory effects.[9] As ADA plays an important role in regulating T cell proliferation and activity, altered blood levels of ADA may indicate immunological dysfunction or rather an immune response to inflammation. This statement is in line with the studies reporting a decrease in inflammatory response with the initiation of treatment reflected in the decrease in ADA activity.[9-12]

Inflammation along with immune dysregulation contributes to pathogenesis and complications of T2DM.[13] ADA may be considered as an important inflammatory biomarker in T2DM, and suppression of ADA activity may lead to attenuation of inflammation and oxidative stress and an improvement in insulin sensitivity.

Table 1: Biochemical parameters in cases and controls

Parameter	Controls (n=30)	Cases (n=30)	p-value
FBG (mg/dL)	96.6 ± 11.2	190.4 ± 73.7	0.001
ADA(IU/L)	22.8 ± 5.6	42.8 ± 15.2	0.001
MDA (µmol/L)	0.67 ± 0.4	3.49 ± 0.53	0.001

Data are expressed as mean ± standard deviation FBG = fasting blood glucose; ADA = adenosine deaminase; MDA = malondialdehyde

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