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Adenosine Deaminase Activity in Type-2 Diabetes Mellitus – An Independent Marker of Glycemic Status and Stimulator of Lipid Peroxidation

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Abstract: Diabetes mellitus is a major worldwide health problem leading to markedly increased mortality and serious morbidity. Literature demonstrates high Adenosine deaminase activity in Type 2 diabetes mellitus than in non- diabetics. This study aims to correlate the association of Adenosine deaminase with dyslipidemia and HbA1C of Type 2 diabetes mellitus patients. A total 140 subjects were taken for study. 60 subjects act as controls (group-A) and 80 type 2 diabetic patients were selected by applying New American Diabetes Association guidelines. Cases were divided into two groups B (n=65 with HbA1C < 10%) and Group-C (n=15 with HbA1C 10%). An elevation of serum Adenosine deaminase was found in diabetic subjects as compared to controls. Adenosine deaminase activity is found to be higher in Group B and Group C. The correlation between Adenosine deaminase and HbA1C is positive and significant in both Group B(r=0.88123; p<0.0001) and C (r=0.972413 p<0.0001), but with dyslipidemia, it is negative in Group B (r=-0.78807; P<0.0001) and non-significant in Group C (r=0.3328; p=0.0035). Adenosine deaminase is elevated in Type 2 diabetes mellitus and can be considered as an independent marker of glycemic status and stimulator of Lipid peroxidation in this population.

Keywords: Adenosine deaminase, Dyslipidemia, Glycated haemoglobin, Glycemic status.

Introduction

Adenosine deaminase (ADA), an enzyme of purine metabolism modulates energy metabolism and is crucial in regulating the steady concentrations of adenosine. Emerging studies have shown ADA as a proinflammatory biomarker of various diseases especially in Immunology, neurological and cardio vascular systems [1-4]. ADA was found as a producer of Reactive oxygen species [ros], stimulator of lipid peroxidation [5, 6], marker of both T-cell activation and glycemic status in Diabetes mellitus (DM), ADA activity is high in lymphoid tissues and it increases lymphocyte proliferation and differentiation [7]

Researches in 1980 used ADA as a diagnostic tool in Meningitis, and T.B. Now it is widely studied because of its importance in Medical field. Gene regulation and gene therapy are being investigated to understand its clinical implications.

Elevated serum ADA were found in obesity, Metabolic syndrome, Type 2 D.M, acute hepatitis, chronic-active hepatitis, liver cirrhosis and hepatoma[8], T.B. brucellosis, Typhoid fever, hypoxic states and cell mediated immunoresponses. [9]

Diabetes Mellitus (DM) is a common endocrinological disorder characterized by the metabolic abnormalities and long term complications. By the year 2030, 80 million people in India would be having diabetes.[10] Adenosine has got insulin like activity on glucose and lipid metabolism particularly in adipose and skeletal muscles. In view of increasing burden of diabetes and mimicing action of adenosine like insulin we studied ADA as a new marker for detecting diabetes and its complications and its association with dyslipidemia and glycemic status (*HbA1c*) in Type 2 D.M.

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Materials and Methods

A hospital based case control study was done on 80 known patients of Type 2 D.M reporting to Santhiram Medical College and Hospital, Nandyal. The patients were divided into Group B n=65 (with *HbA1c* < 10%) and Group-C n=15 (with *HbA1c* > 10%), 60 subjects (Group A) of similar age, (35-75 yr) sex served as controls. The criteria for the diagnosis of D.M were based on American Diabetes Association New guidelines [11]. FBS-100mg/dl, PPBS - < 140 mg/dl and *HbA1c* - < 6%. An exclusion criterion includes Type 1. D.M, acute complications of D.M, GDM, H/O other acute illness and patients on insulin therapy. All the subjects were investigated for FBS, PPBS, *HbA1c*, S.TAG/HDL ratio, S. ADA and with assessment of BMI. Blood sugar was estimated by Glucose oxidase peroxidase (GOD – POD) method, *HbA1c* (Cation exchange resin method) TAG (GPO method), HDL (Direct Immuno turbidometric assay, ADA (Giusti and Galanti) [12] TG/HDL, ratio was calculated which

determines the state of dyslipidemia. BMI was calculated using wt (kg)/height (m^2).

Statistical analysis:

Statistical analysis was done by student't' test using Graph pad software and results were expressed as mean ± SD. Pearson's bivariate correlation analysis was used to correlate each variable with ADA activity. P-value <0.05 were considered as statistically significant.

Results

Table 1 shows the comparison of mean and SD of controls and cases. All parameters taken for study were found to be increased significantly in cases than controls P (<0.0001); thus, showing poor control of blood glucose in diabetic patients as compared to control group.

Table.1: Biochemical Parameters in Controls and Cases

Parameters	Controls (60)	Cases (80)	P-Value
SEX M/F	26/34	32/48	
BMI (kg/m^2)	24.3735±0.998	30.79± 3.428	<0.0001
FBS (mg/dl)	88.3±8.2592	182.45 ± 46.74	<0.0001
PPBS (mg/dl)	118.52±9.29516	256.32 ± 108.05	<0.0001
HbA1c (%)	5.72±1.1022	7.852± 2.230	<0.0001
TG/HDL	3.4±0.3846	4.0425 ± 0.660	<0.0001
ADA (IU/L)	19.9825±3.4141	65.966 ±11.638	<0.0001

BMI- Body Mass Index; FBS-Fasting Blood Sugar; PPBS-Post Prandial Blood Sugar; TG/HDL-Triglyceride/High Density Lipoprotein; ADA – Adenosine Deaminase;

Table 2 shows the comparison of ADA and TG/HDL with different ranges of *HbA1c* to study the effect of Dyslipidemia, hyperglycemia on these patients. Type 2 D.M patients were divided into 2 groups, those with *HbA1c* <10 %and *HbA1c* > 10 %. As *HbA1c* is increased from Group – B to Group -C. ADA levels increased, whereas TG/HDL decreased.

Table.2: Comparison of mean and S.D of ADA and dyslipidemia with different ranges of *HBA1C*

Parameters	Group A	Group B (N=65) *HbA1c*<10%	Group C (N=15) *HbA1c*>10%
ADA	19.9825±3.4141	45.144±18.3918	65.966± 11.63
TG/HDL	3.4±0.3846	4.053±0.75	3.42±0.608

Table 3 shows the comparison of mean and SD of ADA and TG / HDL in various groups. The levels of ADA were found to be significant in all three groups. (P< 0.0001). The levels of TG / HDL were found to be significant in A vs. B but not significant in A vs. C and B vs. C (p<0.8743, p<0.0032) showing that adenosine breaks TAG and releases FFA.

Table.3: Comparison of mean and S.D of ADA and dyslipidemia between the groups

Comparison Of Groups	ADA P-Value	TG/HDL P-Value
A Vs B	<0.0001	<0.0001
A Vs C	<0.0001	<0.8743
B Vs C	<0.0001	<0.0032

Table 4 shows the correlation studies between ADA, TG/HDL *HbA1c* in Group – B and Group-C. ADA has a significant positive correlation with glycemic status in both Group-B (r=0.88123; p<0.0001) and C (r=0.972413; p<0.0001). ADA shows a negative correlation with TG/HDL in Group B (r=-0.78807; P<0.0001) and a non-significant correlation in Group – C (r=0.3328; p=0.0035).

Table.4: Correlation of ADA with *HbA1c* and TGL/HDL in group B & C

Correlation Of Parameters	Group-B	Group-C
ADAVs TG/HDL	-0.78807	0.3328
	P<0.0001	p=0.0035
ADA VS *HBA1C*	0.88123	0.972413
	P<0.0001	P<0.0001

Discussion

The global burden of diabetes is increasing and has reached epidemic proportions worldwide. It is characterized with metabolic abnormalities, like hyperglycemia, itself leading to increased oxidative stress and dyslipidemia. Being a chronic metabolic disorder, its long term complications could have devastating consequences

This study shows female preponderance (60%) than males (40%). About 65% of the cases taken for study had history of diabetes <5yrs. we noted an interesting feature that ADA was found to be elevated in almost 69.2% of patients with <5 yrs of duration of diabetes.

In the present study, the mean serum ADA levels were significantly higher in Group-C (65.966+11.63) than in Group B (45.144+18.39). Similar reports were given by Hoshino T *et al.*, and Kurtal N *et al.*, [12, 13] Type-2 D.M with chronic hyperglycemia favours auto oxidation and also increases free radical activity[14]. Moreover, compared to that of Type-2 D.M patients with relatively good glycemic control *HbA1c* < 10%, ADA activity with poor glycemic control *HbA1c* > 10% was significantly lower. These are in consistent with reports of Lee J G *et al.*, and a study done by Shiva Prakash M *et al.*,[15]

The pathogenesis of increased ADA levels in Type 2 D.M is explained by extra cellular CAMP – adenosine pathway. ADA inactivates adenosine and enhances lipolysis. It also potentiates increase in CAMP accumulation. In the deficiency of insulin,

postprandial lipids and glucose circulate through blood and are taken up by Pancreas, to liver and adipose tissue. The adipocytes stores TAG leading to adipocyte hypertrophy. This exposure leads to cellular dysfunction, increased circulating FFA and a proinflammatory state. Exposure of Hepatocytes to excess fats and glucose leads to steatohepatitis and Insulin resistance. Thus, there is elevation of free fatty acids in diabetes which leads to worsening of IR and β-cell dysfunction. [16- 18]

Chronic Hyperglycemia leads to increased oxidative stress by forming enediol radical and super oxide ions with NADPH oxidase system and increases ADA levels both leading to Insulin resistance. GLUT4 receptors are down regulated in the absence of adenosine. This is one of the reasons for I.R

The Pearson's correlation coefficient between S.ADA, TG/HDL ratio and *HbA1c* in Group-B showed a negative significant correlation with TG/HDL (r=-0.78807; P<0.0001) and a positive significant correlation with *HbA1c*. (r=0.88123; p<0.0001). The same is reported by Reddy M *et al.*, [19] who reported controlled glycemic status with low ADA.

In Group-C ADA vs. TG/HDL is statistically non-significant. (r=0.3328; p=0.0035), but a consistent positive correlation is observed with *HbA1c*. (r=0.972413 p<0.0001). These findings are in accordance with Nisha Subash Chandra Ramani *et al.*, Increased ADA and decreased TG/HDL are because of down regulation of CAMP- Adenosine cascade mechanism and setup of pro-inflammatory state in adipose tissue.

Conclusion

In conclusion, the study shows ADA as an important inclusive prognostic tool, which may be helpful in early detection of complications of Type–2 D.M. ADA is associated with increased levels of *HbA1c*, which plays an important role in determining the glycemic status and derangement of lipid metabolism in diabetes. Further studies are required to support these facts.

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