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TO STUDY THE CORRELATION OF HBA1C WITH SERUM ADENOSINE DEAMINASE ACTIVITY IN TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT

INTRODUCTION

Diabetes Mellitus is the most common endocrinological disorder characterized by metabolic abnormalities and long-term complications. The incidence and the prevalence of Type 2 DM is globally increasing and becoming a major public health problem for health care providers. Adenosine deaminase (ADA) is suggested to modulate the bioactivity of insulin, but its clinical significance in Type 2 diabetes mellitus (DM) is not yet established .The present study was undertaken to evaluate serum ADA activity in patients of Type 2 DM.

AIM AND OBJECTIVE

To determine the serum ADA level and to correlate ADA levels with Blood Glucose, Glycated Hemoglobin (HbA1c) levels in Type-2 DM patients.

MATERIAL AND METHODS

This was a Hospital based comparative cross-sectional study carried out in the Department of Biochemistry atAssam Medical College & Hospital Dibrugarh, Assam, India for a period of 12 months i.e, April 2022 to April 2023. The Relavant history was taken,Clinical examination and laboratory investigations was done on 50 patients of Type 2 Diabetes mellitus, correlation of HbA1c and serum ADA was performed in these individuals taking into consideration the control.

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RESULTS

In the present study population comprised of total of 50 participants diagnosed of T2DM and 50 healthy controls selected from patients attending medicine OPD and also patients admitted in the medicine department for a period of one year from 2022 to 2023.A significant positive correlation was obtained between Serum ADA and HbA1c, Lipid profile, Fasting Plasma Glucose and Post-prandial Glucose respectively.

CONCLUSION

Assessment of Serum ADA level is cost-effective and the efficient use of this biomarker may help in establishing this enzyme as a good marker for assessing cell-mediated immunity in diabetic individuals. Thus, we conclude that elevated ADA activity may be an important indicator in the immuno-pathogenesis of T2DM and can also be implicated as a biomarker for predicting glycaemic control in diabetic individuals.

Keywords: Adenosine deaminase, Glycated Hemoglobin,Fasting Plasma Glucose and Post-prandial Glucose

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia [1]. There is an estimated 143 million people worldwide suffering from diabetes [2], almost five times more than the estimates ten years ago. This number may probably double by the year 2030 [3]. Diabetes is a state characterized by chronic hyperglycaemia resulting from diverse aetiologies, environmental and genetic factors acting together. The long term control of diabetes mellitus is judged by glycosylated haemoglobin which was first isolated by Allen et al [4]. It is formed non-enzymatically by a two step reaction. The levels of HbA1c have increased in diabetic patients and reflected their metabolic control over the past 8-10 weeks [5].

The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. Autoimmune destruction of theβcells of the pancreas with consequent insulin deficiency and abnormalities that result in insulin resistance are the processes involved in the development of diabetes [6]. Also, T2DM has been always pigeon-holed as an intricate metabolic syndrome with multifactorial etiologies. The disease has been characterized by an atypical metabolism of all biomolecules i.e.

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carbohydrates, fats and proteins. Thus, collectively leading to an increased levels of blood glucose and lipid levels within the blood [7,8].

Insulin resistance is associated with low-grade tissue specific inflammatory responses induced by various pro-inflammatory with oxidative stress mediators notably pro-inflammatory cytokines such as Interleukin-1 beta, Interleukin-6, Tumor Necrosis Factors- alpha along with numerous adipocytokines and chemokines, epigenetic factors and other transcriptional and metabolic pathways. Moreover, chronic exposure of pro-inflammatory mediators stimulates the activation of cytokine signaling proteins which ultimately block the activation of insulin signaling receptors in β-cells of pancreatic islets [9,10].

Adenosine deaminase (ADA), an enzyme presents in red cells and the vessel wall catalyses the irreversible hydrolytic deamination of adenosine to inosine and 2'deoxyadenosine to 2'-deoxyinosine. Both inosine and2'-deoxyinosine are converted to hypoxanthine, xanthine and finally to uric acid (UA)[11]. The enzyme exists in two isoenzyme forms: (ADA1 and ADA2) which are coded by eparate genes.[12]ADA is considered as a good marker of cell mediated immunity [13]High lymphocyte ADA activities were found to be elevated in diseases in which there is a cell mediated immune response [14].Chronic hyperglycemialeads to increased oxidative stress by forming enediol radicals and superoxide ions by NADPH oxidase system and increases ADA levels, both leading to insulin resistance [15].

Uric acid is formed by the breakdown of purines and by direct synthesis from 5-phosphoribosyl pyrophosphate and glutamine [16].Hyperuricemia is defined as serum urate level of 6.8 mg/dl (404μmol/litre) [17]. The rising prevalence and incidence of hyperuricemia are probably related to the increased life expectancy of the population, increasing level of obesity, sedentary lifestyles and change in dietary lifestyles. Several epidemiologic studies have reported that high serum levels of uric acid are strongly associated with prevalent health conditions such as obesity, insulin resistance, metabolic syndrome, diabetes, essential hypertension, and renal disease. Even though there are many reports available on serum adenosine deaminase levels and uric acid levels in patients of type 2 diabetes mellitus but no conclusive study could be established [18].

As Diabetes Mellitus is multifactorial in origin and also needs life - long supervision and management so it would be beneficial if some measures could be developed for early diagnosis of the disease on immunological basis, to monitor the glycaemic status

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and or even to initiate proper treatment at the required time to avoid complications. Serum ADA activity estimation may give some light to all these phenomena. Therefore, the present study was conducted to understand the association of serum adenosine deaminase activity in type 2 diabetes mellitus patients and also to find any correlation with glycated haemoglobin and lipid profile in such subject.

MATERIAL AND METHODS

Study design

This was a Hospital based comparative cross-sectional study conducted in the Department of Biochemistry at Assam Medical College & Hospital Dibrugarh, Assam, India

Sample size

Fifty patients diagnosed with T2DM. 50 healthy patients served as control.

Sampling technique

Diabetic patient were selected from medicine OPD by convenient sampling technique and the biochemical parameters was assessed in Department of Biochemistry. Control patients were recruited from routine laboratory (Department of Biochemistry).

Inclusion criteria

Diagnosed type 2 diabetes mellitus patients attending opd and also patients admitted in the Department of Medicine.

Patients were selected on the basis of clinical history, clinical examination and relevant investigation procedures.

- All the cases of 30 years of age and above.
- The individuals were selected irrespective of sex and socio - economic status.
- Voluntary participants with known type2 diabetes mellitus.
- Sex –Male and Female.
- Control –Age and Sex matched Voluntary Healthy subjects.

Exclusion Criteria

- Patients below 30 years of age.

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- Patients who do not give consent for the study.
- Patients on insulin therapy.
- Patients having infection or other ailments.
- Diagnosed type1 diabetes mellitus patients.
- Pregnant women.
- Patients with hepatic disorders, renal failure, acute infections, burns, trauma, acute myocardial infections.

Ethical Clearance was duly obtained from the Ethical Committee.

Laboratory Examination:

SERUM ADENOSINE DEAMINASE ESTIMATION was done by Colorimetric method.

Adenosine deaminase hydrolyses adenosine to ammonia and inosine. The ammonia formed further reacts with a phenol and hypochlorite in an alkaline medium to form a blue indophenol complex with sodium nitroprusside acting as a catalyst. Intensity of the blue coloured indophenol complex formed is directly proportional to the amount of ADA present in the sample.

HbA1c was done byIon Exchange Resin Method [19]. HbA1c is expressed in percentage (%). The normal range is 4.5–6.3%.Glycated haemoglobin (GHb) has been defined operationally as the fast fraction hemoglobins HbA1 (HbA1a, A1b, A1c) which elute first during column chromatography. The non-glycated hemoglobin, which consists of the bulk of hemoglobin, has been designated HbA0. A hemolysate was mixed continuously for 5 minutes with weekly binding cation-exchange resin. The labile fraction is eliminated during the haemosylate preparation and during binding. During this mixing HbAo binds to the ion exchange resin leaving GHb free in the supernatant . After the mixing period a filter separator is used to separate the resin from the supernatant. The percent glycated haemoglobin is determined by measuring absorbance of the glycated haemoglobin (GHb) fraction and the total haemoglobin fraction (THb). The ratio of absorbance of the glycated haemoglobin and the total haemoglobin of the control and the test is used to calculate the percent glycated haemoglobin of the sample.

Fasting blood glucose (FPG) and Postprandial blood glucose (PPG) was performed by GOD/POD Method (Microlab 300SemiAutoanalyser). FPG and PPG was expressed in

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mg/dl. DM was classified as Controlled and Uncontrolled on the basis of HbA1c level (< 7% = Controlled & > 7% = Uncontrolled) respectively.

Statistical analyses: The results were expressed as Arithmetic Mean ± Standard Deviations (SD) and analysed by unpaired Student's t test on continuous measurements and results on categorical measurements were presented in Number (%). Pearson coefficient of correlation was used to find out the correlation between different parameter.

RESULTS

The study population comprised of total of 50 participants diagnosed of T2DM and 50 healthy controls selected from patients attending medicine OPD and also patients admitted in the Medicine department for a period of one year from 2022 to 2023.

Table 1: represents the Age wise distribution among cases of diabetes patients and control group. Itwas observed that maximum number of cases were in the agegroup of 41-50 years constituting 36% of cases,followed by 34% of cases in the age group of 51-60years.

AGE GROUP	**CASES**		**CONTROLS**	
	No.	%	No.	%
30-40	8	16.0	8	16.0
41-50	18	36.0	18	36.0
51-60	17	34.0	17	34.0
61-70	4	8.0	4	8.0
>70	3	6.0	3	6.0
Total	50	100.0	50	100.0

TABLE .1 AGE WISE DISTRIBUTION OF CASESANDCONTROLS

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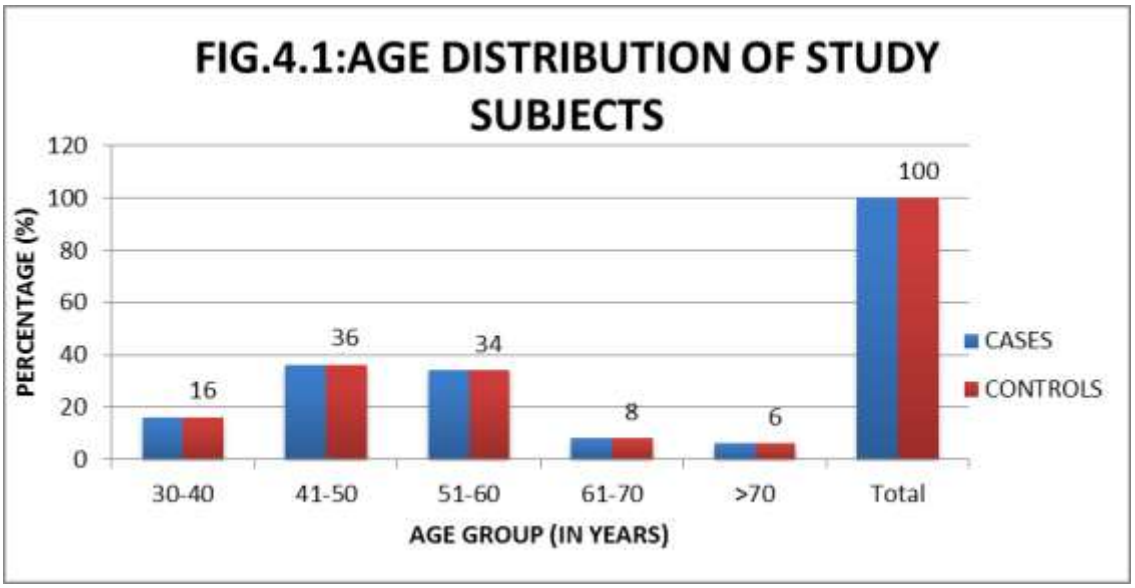

GRAPH .1 AGE WISE DISTRIBUTION OF STUDY SUBJECTS.

Table 2: represents the Male: Female ratio for all subjects of the study. It was observed that 58% cases were males and 42 % cases were females with male to female ratio of 1.38:1.

GENDER	CASES		CONTROLS	
	NUMBER	PERCENTAGE (%)	NUMBER	PERCENTAGE (%)
MALE	29	58	29	58
FEMALE	21	42	21	42
TOTAL	50	100	50	100

TABLE 2: GENDERWISE DISTRIBUTION OF CASES AND CONTROLS.

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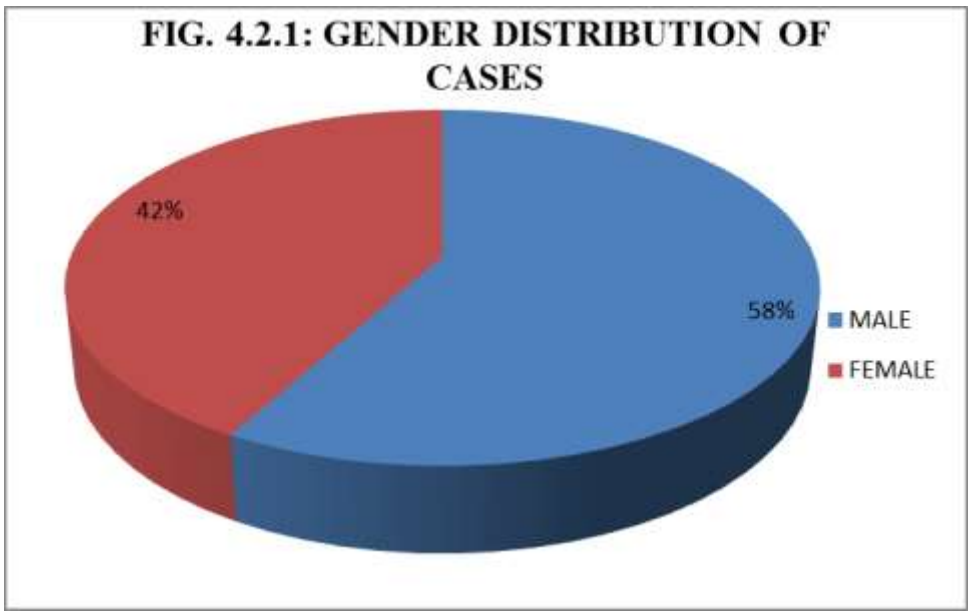
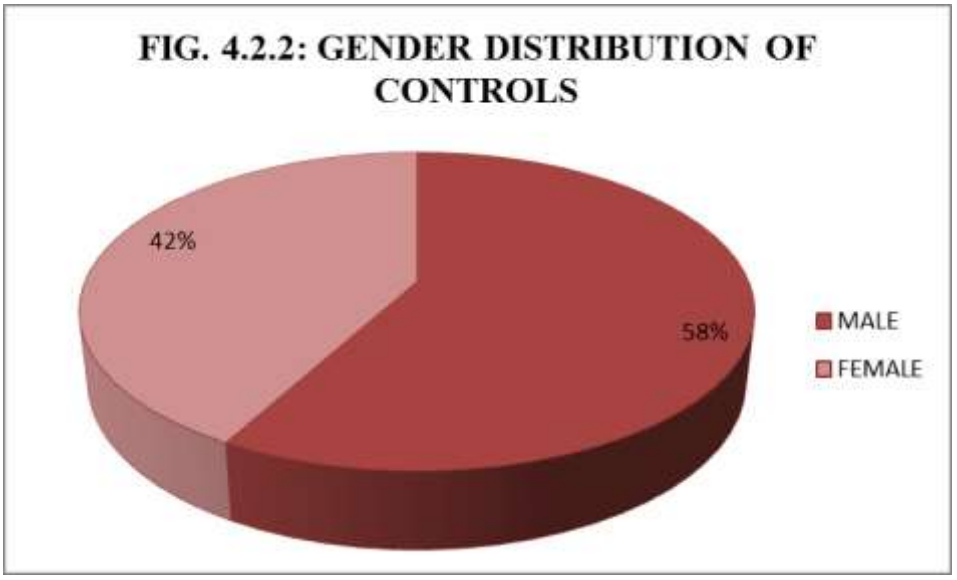


GRAPH 2: GENDER WISE DISTRIBUTION OF CASES.



GRAPH 3: GENDER WISE DISTRIBUTION OF CONTROLS PATIENTS.

It was observed from Table-3 that the mean concentrations of fasting blood glucose and post prandial blood glucose in cases were higher than that in controls and it was statistically very highly significant($p<0.001$).

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STUDYGROUP	**NUMBERS**	**FASTINGBLOOD GLUCOSE (mg/dl)**	**POST-PRANDIAL BLOOD GLUCOSE (mg/dl)**
CASES	50	167.2 ±73.51	268.4 ± 107.90
CONTROLS	50	88.3 ± 13.27	122.02 ± 11.51
p VALUE		<0.001	<0.001

TABLE 3: SHOWING MEAN LEVEL OF FASTING BLOOD GLUCOSE AND POST PRANDIAL BLOOD GLUCOSE IN STUDY SUBJECTS.

AGE GROUP	**CASES**		**CONTROLS**		**pVALUE**
	RANGE	**MEAN±SD**	**RANGE**	**MEAN±SD**	
30-40	18.0-65.0	37.4±14.9	16.0-20.0	17.67±1.70	<0.01
41-50	21.92-104.16	40.65±18.68	14.60-32.0	21.39±5.19	<0.01
51-60	23.70-75.0	39.10±13.22	15.20-32.00	21.36±4.06	<0.01
61-70	24.0-69.0	39.07±20.46	14.0-18.0	15.90±1.65	<0.01

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>70	28.0-57.0	40.67±14.84	16.60-55.00	30.87±21.02	>0.05
Total	18.00-104.16	39.48±15.68	14.0-55.0	20.91±6.58	<0.001

TABLE -4: AGE DISTRIBUTION OF SERUM ADA IN STUDY PARTICIPANTS

It was observed from Table-5 that the highest mean value of serum ADA activity was found in the age group above 70 years in the cases and lowest in the age group 30-40 years. The highest mean value of ADA activity in the controls was in the age group above 70 years.So,in both the study groups highest activity was found in the age group above 70 years.But the difference in mean values between cases and controls in the age group above 70 years was statistically not significant (p>0.05).

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Overall,the mean serum ADA concentration in cases was 39.48±15.68 and in controls was 20.91 ± 6.58 and it was statistically very highly significant (p<0.001).

STUDY GROUP	**SERUMADA(U/L)**				**SIGNIFICANCE**
	RANGE		**MEAN±SD**		
	MALE	FEMALE	MALE	FEMALE	p value
CASES	18.00±104.16	21.92±75.00	38.59±17.16	40.71±13.67	>0.05
CONTROLS	14.60±55.00	14.0±32.0	21.67±7.78	19.87±4.42	>0.05

TABLE-5: GENDER DISTRIBUTION OF SERUM ADA IN STUDY SUBJECTS

It was observed from Table-6 that the mean serum ADA activity in male cases was 38.59±17.16and in female cases was 40.71±13.67.

The mean serum ADA activity in male controls was 21.67 ± 7.78 and in female controls was 19.87 ±4.42.

The difference in the mean serum ADA between males and females in cases as well as in controls was very minimal and it was statistically not significant (p>0.05).

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PARAMETER	**FBG**		**PPBG**	
ADA	rvalue	pvalue	rvalue	pvalue
	0.47	0.005	0.69	<0.001

TABLE-6: PEARSON CORRELATION OF BLOOD GLUCOSE PARAMETERS WITH SERUM ADA IN CASES.

It was observed from Table 7 that there was positive correlation between serum ADA activity with blood glucose levels both fasting and postprandial with rvalues of0.47 for fasting and 0.69 for post-prandial in type 2 diabete smellitus patients.

SIGNIFICANCE	**CASES**		**CONTROLS**	
	RANGE	**MEAN+SD**	**RANGE**	**MEAN+SD**
	4.21-12.93	8.65 ± 2.28	3.96-6.47	5.48 ± 0.63
p VALUE	<0.001			

TABLE-7: SHOWING RANGE AND MEAN VALUES OF HbA_{1C} IN STUDY SUBJECTS

In our study, the mean value of HbA1C of cases was more than controls and it was statistically very highly significant.

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STUDY GROUP	**GLYCATEDHAEMOGLOBIN**				**SIGNIFICANCE**
	RANGE		**MEAN±SD**		
	MALE	**FEMALE**	**MALE**	**FEMALE**	**p value**
CASES	4.21-12.84	5.39-12.93	8.55±2.50	8.78±1.99	>0.05
CONTROLS	4.55-6.47	3.96-6.47	5.60±0.57	5.31±0.69	>0.05

TABLE-8: GENDER DISTRIBUTION OF HbA1C% IN STUDY SUBJECTS

In our study, it was seen that there was difference between the mean values of males and females in cases and controls and it was statistically not significant p>0.05.

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HbA1c RANGE(%)	**NO. OF CASES**	**MEAN±S.D.**		**SIGNIFICANCE**
		HbA1C(%)	**SERUMADA(U/L)**	**pVALUE**
<6	7	5.45±0.60	25.25±2.90	
6.00-7.50	10	6.77±0.33	32.33±5.73	
7.51-9.00	14	8.29±0.46	39.14±10.89	
9.01-10.50	8	9.87±0.57	41.74±10.75	
10.51and above	11	11.95±0.70	53.81±22.62	
Overall	50	8.65±2.28	39.48±15.68	<0.001
PearsonCorrelationCoefficient(r)			0.57	

TABLE-9: SHOWING THE CORRELATION BETWEEN GLYCATED HEMOGLOBINANDSERUMADAACTIVITYINDIABETICPATIENTS

It was observed from Table9 that the cases in the HbA1C range of 10.51 and above have the highest mean of ADA concentration i.e. ,53.81+22.62 and HbA1C in the range below 6 have the lowest mean ADA concentration i.e.,25.25+2.90. It was seen that serum ADA activity increased with increase in the glycated haemoglobin level and it was very highly significant ($p< 0.001$).

DISCUSSION:

Diabetes Mellitus is a group of metabolic disease characterised by hyperglycaemia

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resulting from a defect in insulin secretion, insulin action, or both. The current study "A study of serum adenosine deaminase activity in type2 diabetes mellitus"-was based on the estimation of serum adenosine deaminase activity in type 2 diabetes mellitus patients and also to find any relation of serum ADA with glycated haemoglobin levels [19,20].

T2DM is the predominant form of diabetes worldwide, accounting for 90% of cases globally. It is a multifactorial systemic disease with hereditary and environmental causes being the major attributable factor. These lead to insulin resistance and defective secretion of insulin by pancreatic beta-cell. Immunological disturbances of cell-mediated origin are believed to initiate from T-lymphocyte dysfunction. Invitro studies have shown that in T2DM, inappropriate immune responses may result from the defects in the action of insulin that is required for the function of T-lymphocytes . ADA plays a crucial role in lymphocyte proliferation and differentiation and shows its highest activity in T- lymphocytes [20, 21].

In the present study 100 participants, including 50 cases and 50 controls subjects were enrolled, in which maximum numbers of cases and controls were in the age group of 41-50 years (36%) followed by 34% of cases and controls in the age group of 51-60 years and least of cases are found in age group >70 (6.0%). This finding was similar to other studies by research investigator Supriya Singh et al (2020) [22] in which the mean age of subjects in the diabetic cases as well as control group was between 41 – 60 years of age . other similar finding by Kundu D et al (2019)[23] in which maximum numbers of cases and controls were in the age group of44.0 ± 5.1 and 43.2 ± 6.0 respectively .other similar study by A.Niraula (2018)[24] in which the maximum numbers of cases and controls were in the age group of 54.82±12.16 and 45.5±10.4 respectively.

In the present study it was found that 58% cases have been males and 42% caseshavebeenfemaleswithmaletofemaleratioof1.38:1. This finding is in accordance with the study conducted by Supriya Singh et al (2020) [22] in which the male: female distribution in control group was 56: 44 whereas in Diabetic group it was 67: 33 respectively. And similar finding by AmandeepKaur et al (2012)[25] in which female preponderance (60%) than males (40%) respectively.

ADA is an ectoenzyme expressed in higher level in lymphoid tissue. Since the enzyme catalyzes the irreversible deamination of adenosine to inosine, it has an

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important role in regulating adenosine concentration ADA is an ectoenzyme expressed in higher level in lymphoid tissue. Since the enzyme catalyzes the irreversible deamination of adenosine to inosine, it has an important role in regulating adenosine concentration.

In the present study it was found that the mean serum ADA activity in male cases is 38.59± 17.16 and in female cases is 40.71 ± 13.67 and in controls group of male is 21.67± 7.78 and in female was 19.87± 4.42 respectively. This finding was in accordance with other study by A.Niraula (2018) [24] ,Aishwarya R (2022) [26] and Supriya Singh et al (2020) [22] respectively.

In the present study, it was seen that the mean value of glycated haemoglobin in male cases was 8.55±2.50 and in female cases was 8.78±1.99 and in the controls group the mean values of glycated haemoglobin in male controls was recorded to be 5.60±0.57and in female controls was 5.31±0.69.This finding was in support with the study conducted by A.K AI- Miraj et al (2021) [27] in which the mean glycated haemoglobin in control in controls group 5.13± 0.57 and cases group 7.98± 1.13 repectively. The similar finding by Samdani TS et al (2017) [28] andSupriya Singh et al (2020) [22] respectively.

In the present study, it was observed that the cases in the HbA1C range of 10.51and above have the highest mean of ADA concentrationi.e.,53.81+22.62 and HbA1C in the range below 6 have the lowest mean ADA concentrationi.e.,25.25+2.90. Hence,it is seen that the serum ADA activity increases with increase in the level of glycated haemoglobin. The Pearson Correlation coefficient“r”was 0.57 which also established the fact that there was positive correlation of serum ADA activity with glycated haemoglobin level.This finding was in accordance with the study conducted by Aishwarya R (2022) [26] in which the mean ± SD of HbA1C was 9.85± 2.73.Mean ± SD of serum ADA levels was 40.39 ± 4.69. Spearman's correlation coefficient in our study was 0.728 indicating a strong correlation between serum ADA and HbA1C. There was a linear correlation between HbA1C levels and serum ADA and the correlation was statistically significant P Value;0.001. other similar finding byA. Niraula (2018)[24] in which the mean ± SD of HbA1C was 6.78±2.48 and 3.4±0.55 and mean ± SD of serum ADA levels was40.44±17.97 and 10.55±2.20. There were other similar finding by Kundu D et al (2019)[23]which showed positive correlation between HbA1c and ADA (r=0.122).It is concluded that there is an increase in serum ADA levels with increase in

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HbA1c levels.

In the present study it was found that there was difference between the means of blood glucose levels both fasting and postprandial between cases and controls and it was statistically very highly significant. There was difference in the mean values of serum lipid profile in cases and controls and it was statistically significant. This finding was similar to the study conducted by other authorsSamdani TS et al (2017) [28] , A.K AI- Miraj et al (2021) [27],A. Niraula (2018)[24] ,Chellamma Jayakumari (2020)[29] and Kundu D et al (2019)[23]respectively.

Increased ADA level can be used to determine the glycemic status in the patients of type 2 DM and serve as a marker for insulin resistance.Metabolic and immunological disruption are two critical components in type 2 diabetes mellitus, a primary cause of morbidity and mortality.ADA is an enzyme that is regarded a useful marker of cell-mediated immunity [30].

CONCLUSION:

The study showed that the serum ADA activity is significantly increased in clinically diagnosed type 2 diabetes mellitus patients in comparison to healthy individuals. Moreover, there wasa significant increase in the serum ADA activity in the cases with poor glycaemic status i.e., increased HbA1c levels. However, the proper mechanism of how ADA activity increases in type 2 diabetic patients is not clear. So further studies would be required to consider ADA as a pathogenic or a prognostic marker of type 2 diabetes with a larger sample size and longer duration of time and also to find any direct relationship between insulin treatment and serumADA activity to find whether serum ADA levels can be used to initiate insulin therapy in type 2 diabetic patients.

Declarations:

Conflicts of interest: There is no any conflict of interest associated with this study

Consent to participate: We have consent to participate.

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Consent for publication: We have consent for the publication of this paper.

Authors' contributions: All the authors equally contributed the work.

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