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Hyperuricemia in Type 2 Diabetes Mellitus

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Abstract- Recently there has been a growing interest in the association of uric acid levels with hyperglycemia. Insulin deficiency or subnormal functioning of insulin may induce possible alterations in purine nucleotide metabolism, specifically uric acid turnover. Studies have indicated that a close relationship do exists between plasma uric acid levels and glucose utilisation in type 2 diabetes mellitus. Though there are reports showing elevated plasma uric acid levels in type 2 diabetes mellitus but the origin of raised uric acid is still obscure. Hence a study was undertaken to assess the origin of raised plasma uric acid levels in diabetes mellitus. The type 2 diabetic subjects attending the OPD of Subbaiah Medical College Hospital, Purale, Shimoga were randomly selected. A fasting Blood sample was collected and the plasma samples were employed for estimation of glucose, uric acid, adenosine deaminase and 5'-nucleotidase levels. The results indicate a parallel raise in the plasma levels of adenosine deaminase and in 5'-nucleotidase along with plasma uric acid levels in type 2 diabetic subjects suggesting the raised plasma uric acid in type 2 diabetic subjects is due to increased purine catabolism.

Keywords: *type 2 diabetes mellitus, plasma uric acid, ada, 5'-nucleotidase.*

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Hyperuricemia in Type 2 Diabetes Mellitus

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Abstract- Recently there has been a growing interest in the association of uric acid levels with hyperglycemia. Insulin deficiency or subnormal functioning of insulin may induce possible alterations in purine nucleotide metabolism, specifically uric acid turnover. Studies have indicated that a close relationship do exists between plasma uric acid levels and glucose utilisation in type 2 diabetes mellitus. Though there are reports showing elevated plasma uric acid levels in type 2 diabetes mellitus but the origin of raised uric acid is still obscure. Hence a study was undertaken to assess the origin of raised plasma uric acid levels in diabetes mellitus. The type 2 diabetic subjects attending the OPD of Subbaiah Medical College Hospital, Purale, Shimoga were randomly selected. A fasting Blood sample was collected and the plasma samples were employed for estimation of glucose, uric acid, adenosine deaminase and 5'-nucleotidase levels. The results indicate a parallel raise in the plasma levels of adenosine deaminase and in 5'-nucleotidase along with plasma uric acid levels in type 2 diabetic subjects suggesting the raised plasma uric acid in type 2 diabetic subjects is due to increased purine catabolism.

Keywords: type 2 diabetes mellitus, plasma uric acid, ada, 5'-nucleotidase.

I. Introduction

Insulin deficiency as observed in type-2 diabetes mellitus apart from inducing disturbances in glucose and fat metabolism may also cause possible alterations in nucleotide metabolism, specifically in uric acid turnover. Uric acid, the end product of purine metabolism, is produced by the degradation of purine nucleotides and purine nucleosides with the help of degradativeenzymes, 5' Nucleotidaseadenosinedeaminase, nucleosidephosphorylase and xanthine oxidase. Since the time our pioneer observation regarding the raised blood uric acid levels in diabetic subjects (1), many reports have appeared showing a relationship of plasma uric acid levels with hyperglycemia (2-17). Many research workers (2-15) suggest a positive correlation between plasma uric acid levels and diabetes mellitus while few reports advocate no such correlation (16,17). The specific observation of Feldmann & Lebrovitz (18), that ammonium ion (NH_4^+) do modulate the glucose induced insulin secretion /action relates nucleotide metabolism to insulin action, as ammonia is a bye-product of purine nucleotide degradation.

Hence a study was planned to reassess the plasma uric acid levels in diabetic subjects as well as to establish the possible origin of the raised plasma uric acid levels in type 2 diabetic subjects.

II. Materials and Methods

All the chemicals and reagents employed in the present study were of analar grade, and the adenosine as well as AMP (Adenosine mono phosphate) (kindly donated by Dr. Aski, B M Patil Medical College, BLDE University, Bijapur, Karnataka, India) were of chromatographic purity.

The type 2 diabetic subjects(both sexes) attending the medical OPD of Subbaiah Medical College Hospital ,Purle, Shimoga, who were in the age group of 30-60 years were randomly selected. Age matched normal subjects were selected from the employees of medical college and from medical college hospital. The subjects having orthopedic problems were excluded from the study. A fasting blood sample from both the normal as well as diabetic subjects were collected (4-5ml) with heparin as an anticoagulant after obtaining an informed consent from them. These blood samples were centrifuged for about 6-8 minutes at 3500rpm.

The separated clear plasma was employed for estimation of glucose (19), uric acid (20), Adenosine deaminase (ADA) (21) and 5'-Nucleotidase (22) levels. The results obtained were statistically analysed and the significance were calculated using Student't' test.

III. Results

A total number of 224 subjects including 120 diabetic and 104 normal subjects were employed in the present study. The diabetic subjects included 72 male diabetics and 48 female diabetic subjects. The normal subjects included 60 male and 44 female subjects. These diabetic subjects when divided age wise, there were 52 diabetic subjects in the age group of 30-50years and 68 diabetic subjects were above the age of 50years. Further these diabetic subjects were including 61 diabetics with positive family history of diabetes and 63 without family history of diabetes. This distribution of subjects are given in chart 1. The results obtained in the present study are depicted in table 1 to table 6.

Table 1 narrates the plasma levels of glucose, uric acid, ADA and 5'-Nucleotidase in normal subjects and in type 2 diabetic subjects. It is evident from the table that a significant raise is seen in plasma levels of

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uric acid(P>0.001), ADA (P>0.001), and 5'-Nucleotidase (P>0.001), in diabetic subjects as compared to normal subjects suggesting that the raise in uric acid level is due to increased degradation of purine nucleotides & nucleosides.

Table 1 : Table showing the levels of glucose, uric acid, 5'-nucleotidase and adenosine deaminase in plasma in normal and diabetic subjects

	Glucose mg. %	Uric acid mg.%	Adenosine deaminase units/L.	5'-Nucleotidase units/100ml.
Normal Subjects (104)	78.6 ± 16.4	5.80 ± 1.20	12.62 ± 4.22	7.0 ± 0.08
Diabetic Subjects (120)	226.40*** ± 28.3	11.8*** ± 2.10	28.12*** ± 8.61	37.5*** ± 11.25

Note: 1. The number in parenthesis shows the number of samples
2. Values are expressed as their Mean + S
*3. p- value*p<0.05, *p<0.01, *** p< 0.001.*

Table 2 gives the plasma levels of glucose, uric acid,ADA and 5'-Nucleotidasein normal male subjects and in type 2diabetic subjects. It is clear from the table that all the parameters studied are significantly elevated in male diabetic subjects as compared to normal male subjects(p>0.001).

Table 2 : Table showing the plasma levels glucose, uric acid, adenosine deaminase, 5'-nucleotidase in normal male subjects and type 2 diabetic male subjects.

	Glucose mg/dl	Uric acid mg/dl	Adenosine deaminase units/L.	5'-Nucleotidaseunits/100ml.
Normal male subjects (60)	72.20 ± 12.42	5.62 ± 1.18	12.20 ± 3.60	6.8 ± 1.0
Diabetic male subjects (72)	208.80*** ± 16.12	10.82*** ± 2.22	27.90*** ± 7.80	36.0*** ± 9.0

Note: 1. The number in parenthesis shows the number of samples
2. Values are expressed as their Mean + SD
*3. p value*p<0.05, *p<0.01, *** p< 0.001.*

Table 3 gives the plasma levels of glucose, uric acid,ADA and5'-Nucleotidase in normal female subjects and in type 2diabetic female subjects. It is evident from the table that all the parameters studied are significantly elevated in diabetic female subjects as compared to normal female subjects(p>0.001).

Table 3 : Table showing the plasma levels glucose, uric acid, adenosine deaminase and 5'-nucleotidase in normal female subjects and type 2 diabetic female subjects

	Glucose mg/dl	Uric acid mg/dl	Adenosine deaminase units/L.	5'-Nucleotidase units/100ml.
Normal female subjects (44)	74.80 ± 6.80	5.62 ± 1.22	11.80 ± 2.10	7.0 ± 2.2
Diabetic female subjects (48)	212.62*** ± 12.20	11.30*** ± 1.80	28.20*** ± 6.60	37.1*** ± 6.60

Note: 1. The number in parenthesis shows the number of samples
2. Values are expressed as their Mean + SD
*3. p- value*p<0.05, *p<0.01, *** p< 0.001.*

Table 4 gives the plasma levels of above parameters in type 2 male diabetic subjects & in type 2 female diabetic subjects. It is clear from the table that no variation in the parameters studied were observed in male diabetics ascompared to femalediabetic subjects.

Table 4 : Table showing the variation of glucose , uric acid, adenosine deaminase and 5'-nucleotidase in plasma in diabetic male subjects and diabetic female subjects

	Glucose mg. %	Uric acid mg.%	Adenosine deaminase units/L.	5'-Nucleotidase units/100ml.
Diabetic male Subjects (72)	208.80 ± 16.12	10.82 ± 2.22	25.84 ± 5.36	36.0 ± 9.00
Diabetic Female subjects (48)	212.62 ± 12.20	11.30 ± 1.80	28.20 ± 6.60	37.10 ± 6.60

Note: 1. The number in parenthesis shows the number of samples
2. Values are expressed as their Mean + SD
*3. p- value*p<0.05, *p<0.01, *** p< 0.001.*

Table 5 & Table 6 narrates the plasma levels of glucose, uric acid,ADA and 5'-Nucleotidase in diabetic subjects of 30-50years of age group and in diabeticsubjects above the age of 50years(Table 5)as well as in diabetic subjects with positive family history of diabetes mellitus and in diabeticsubjects without any family history of diabetes mellitus (Table 6). As seen from the tables no significant variations observed between diabeticsubjects of different age groups as well as between the diabeticsubjects with positive family history of diabetes mellitus as compared to diabeticsubjects without any such diabetic history.

Table 5 : Table showing the variation of glucose , uric acid, adenosine deaminase and 5'-nucleotidase in plasma in diabetic subjects with different age group

Age Group	Glucose mg. %	Uric acid mg.%	Adenosine deaminase units/L.	5'-Nucleotidaseunits/100ml.
30-50 Years (52)	210.6 ± 16.8	11.7 ± 3.10	25.02 ± 4.82	27.0 ± 5.50
Above 50 Years (68)	222.4 ± 22.6	11.6 ± 3.32	22.88 ± 5.66	26.5 ± 6.00

Note: 1. The number in parenthesis shows the number of samples
2. Values are expressed as their Mean + SD
*3. p- value*p<0.05, *p<0.01, *** p< 0.001.*

Table 6 : Table showing the variation of glucose , uric acid, adenosine deaminase and 5'-nucleotidase in plasma in diabetic subjects with or without family history of Diabetes mellitus.

Age Group	Glucose mg. %	Uric acid mg.%	Adenosine deaminase units/L.	5'-Nucleotidase units/100ml.
Diabetics with family history (61)	208.8 ± 18.6	10.9 ± 2.80	28.12 ± 5.16	28.5 ± 6.90
Diabetics Without family history (63)	220.6 ± 22.8	10.8 ± 1.20	26.32 ± 4.12	30.5 ± 5.80

Note: 1. The number in parenthesis shows the number of samples
2. Values are expressed as their Mean + SD
*3. p- value*p<0.05, *p<0.01, *** p< 0.001.*

IV. Discussion

Starting with the first observation (1), showing the increased whole blood uric acid levels in diabeticsubjects, several reports have been presented suggesting a relationship between the uric acid levels and hyperglycemia in diabetic subjects (2-17). Many reports advocating a raise in plasma uric acid levels in diabetic subjects (2-15) while few negate such observation (16, 17). The significant enzymes, which are quite abundant in tissues, responsible for the purine degradation are Adenosinedeaminase (Adenosine amino hydrolase EC: 3, 5, 4, 4) and 5'- Nucleotidase (5' nucleotide phosphohydrolase EC: 3, 1, 3, 5). Adenosinedeaminase is implicated in inflammatory conditions as well as in micro and macro vascular complications of diabetes mellitus (23). Similarly 5' nucleotidase has been claimed elevated in type 2 diabetes mellitus (24). Adenosine mimics the action of insulin on glucose and lipid metabolism in adipose tissue as well as in myocardium, while it inhibits the insulin effect on total hepatic glucose output suggesting that adenosine causes local insulin resistance in liver tissue. Adenosine modulates the action of insulin on various tissues differently and its tissue concentration is affected by ADA levels (25, 26). A parallel rise in the enzyme activities of adenosine deaminase and 5'-Nucleotidase in plasma, which may be due to an increase in their levels in the tissues, along with a rise in plasma uric acid levels suggest that the rise in plasma uric acid observed in the present study in type 2 diabetic subjects may be due to increased degradation of purine nucleosides and nucleotides. Kurtul N etal (27)have shown increased level of serum ADA activity in type 2 diabetic subjects with its correlation to HbA1c and suggested that ADA is important enzyme for modulating the bioactivity of insulin.

Subnormal insulin levels or insulin resistance seen in type 2 diabetes mellitus may decrease the activity of many glycolytic and citric acid cycle enzymes as insulin is a known promoter of the activities of pyruvatedehydrogenase, hexokinase, phosphofructok-inase, pyruvatekinase, α-ketoglutaratedehydrogenase etc (28). Such a decrease in the activity of these enzymes leads to accumulation of glucose-6-phosphate, which may be channeled through HMP pathway causing an increase in ribose-5-phosphate which is the starting compound for purine biosynthesis. Thus purine synthesis increases resulting in an elevated formation of uric acid.

It is known that the end regulation of insulin action is achieved through regulating protein-tyrosine phosphstases (PTP) which are thiol enzymes (29, 30, 31). One of the optimistic speculation is that the tissues and cells do try to adjust to the insulin deficiency state by prolonging the insulin action through regulating these PTPs by generating little amount of free oxygen species and these oxygen species in turn try to slow down the activity of PTPs by reacting with their free thiol groups. A possible reaction to generate oxygen species is purine degradation. A rise in plasma uric acid levels seen in the present study in type 2 diabetic subjects do support this speculation. This rise in plasma uric acid levels in diabetic subjects may also due to deterioration of glucose metabolism which is primarily due to insulin insufficiency as it is suggested by many research workers that increased plasma uric acid levels do correlate with deterioration of glucose metabolism in type 2 diabetic subjects(32,33).

The rise in plasma uric acid levels in type 2 female diabetic subjects is more pronounced as compared to type 2 male diabetic subjects (ref table 4) is in agreement with the earlier reports (34, 35) and which may be due to estrogen, as estrogen is known to influence secretion of adrenal steroids which inturn influences the catabolism of nucleotides and nucleic acids (36, 37). No much variations are seen in the levels of uric acid, ADA and 5'-Nucleotidasein diabetic subjects of 30-50 yrs of age group as compared to diabetic subjects of above 50yrs age group (ref table 5) as well between diabetic subjects with positive family history as compared to diabetic subjects without any diabetic family history (ref table 6).

It is concluded from the results of the present study in type 2 diabetic subjects that there is a definite rise in plasma uric acid levels in these diabetic subjects as compared to their normal counterparts and the uric acid elevation is due to increased degradation of purines as evidenced by the rised activity of Adenosine deaminase and 5'-Nucleotidase.

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CHART -1

Chart showing the distribution of normal and diabetic subjects according to various parameters.

Total number of subjects in the present study	------224
Total number of normal subjects	----- 104
Normal males	------60
Normal females	----- 44
Total number of Type 2 diabetic subjects	------120
Male diabetes	------72
Female diabetes	------48
Diabetic subjects in the age group of 30—50yrs	------52
Diabetic subjects above 50yrs of age	------68
Diabetic subjects with positive family history of diabetes	------61
Diabetic subjects without positive family history of diabetes	----63