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TO STUDY THE LEVEL OF SERUM URIC ACID IN HEALTHY AND DIABETIC PATIENTS, URIC ACID: A PREDIABETIC MARKER

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ABSTRACT

Introduction: In India about 39% of the population is suffering from obesity among which approx. 11% are diabetic and nearby 15% are pre-diabetic. These metabolic disorders are somehow related to the production of reactive oxygen species in individuals.The production of excessive amounts of Reactive oxygen species is responsible for development of many diseases including Diabetes, Neurodegenerative Disorders, Cancer etc. Uric acid is also a Reactive oxygen species although along with it also shows antioxidants property, the formation of uric acid normally takes place as end product of purine metabolism. We hypothecally sate that there is correlation in diabetes and uric acid metabolism.

Aim and Objective: This study was conducted to identify the correlation of Serum Uric Acid (SUA), in diabetic and healthy individuals.

Material andMethods: A total of 150 blood samples were collected and all the samples were analysed for FBG by the GOD-POD Method and HbA1c Method. The samples were analysed for Serum Uric Acid (SUA) by Uricase enzymatic Method concentrations that were used for correlative study.

Results: In the present study it was observed there was a significant difference in the value of serum uric acid in all different groups.

Conclusion: The Study showed correlation of HbA1c, SUA in Diabetic, Pre-Diabetic &NonDiabetic conditions.

Keywords: Pre- Diabetic, Diabetic, Glycosylated haemoglobin, Serum Uric Acid.

Introduction

Diabetes mellitus (DM) is one of the first diseases identified by humans. The first known reference to it dates back to an Egyptian document from around 3000 BCE (1). In 1936, a definitive division between type 1 and type 2 diabetes was identified (2). Type 2 diabetes was first recognized as part of the metabolic syndrome in 1988 (3). Type 2 diabetes is the most commonly observed form of this medical condition, distinguished by the presence of hyperglycaemia, insulin resistance, and a relative insufficiency of insulin. Type 2 diabetes was first referred to as non-insulin dependent diabetes (4).

The occurrence of type 2 diabetes is attributed to the intersection of genetic, environmental, and behavioural risk factors (5, 6). According to projections, the prevalence of diabetes mellitus (DM) was estimated to be 366 million individuals in 2011, and it is anticipated to rise to 552 million by the year 2030. The prevalence of type 2 diabetes is on the rise in every country, with a majority of 80% of affected individuals residing in low- and middle-income nations. The incidence of type 2 diabetes varies significantly among regions due to a combination of environmental and behavioural risk factors (7), (8,9).

According to the guideline of AMERICAN ASSOCIATION SOCIETY OF DIABETES (10,11)-
1) The HbA1C level≥ 6.5%.
2) A fasting plasma glucose concentration over 126 mg/dl,fasting is defined as no caloric intake for at least 8 hours.
3) An oral glucose tolerance test involving the administration of a 75 mg glucose load and the assessment of a 2-hour glucose level that is greater than or equal to 200 mg/dl.
According to the guideline of AMERICAN ASSOCIATION SOCIETY OF Pre-DIABETES
1) The HbA1C level 5.7-6.4 %.
2) A fasting plasma glucose concentration over 100-125 mg/dl,Fasting is defined as no caloric intake for at least 8 hours.
3) An oral glucose tolerance test involving the administration of a 75 mg glucose load and the assessment of a 2-hour glucose level that is greater than or equal to 140-199 mg/dL.

Variable	**Non-DIABETES**	**Pre-DIABETES**	**DIABETES**
HbA1c (%)	<6.0 %	6.0-6.4 %	≥ 6.5%
FBG (mg/dl)	<110 mg/dl	110-125 mg/dl	≥ 126 mg/ dl
PPBG(mg/dl)	<140 mg/dl	140-199 mg/dl	>200 mg/ dl

Table 1.1 shows the WHO Guidelines of Blood Sugar Parameter (12, 13)

Patients presenting with symptoms consistent with diabetes mellitus do not require further diagnostic tests for confirmation of the condition.
The levels of HbA1C can be influenced by factors that either prolong or decrease the lifespan of red blood cells (RBCs). Anaemia has been found to result in falsely elevated HbA1C values, whereas treatment has been observed to lead to falsely lowered HbA1C readings (14). The individual's glycated haemoglobin (HbA1c) level is measured at 5.7%, indicating the presence of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

Uric acid

Uric acid is the final by-product of purine metabolism within the human body. The production of this substance occurs within the hepatic organ. Purine nucleotides undergo decomposition, resulting in the formation of hypoxanthine and guanine. A portion of these compounds can be recycled and undergo phosphorylation to form hypoxanthine nucleotides. The remaining portion is metabolized through the enzymatic reaction catalysed by xanthine dehydrogenase/oxidase (XDH/XO), ultimately leading to the production of uric acid. The expression of XDH/XO is primarily observed in the parenchymal cells of the liver and small intestine. Xanthine dehydrogenase (XDH) exhibits a relatively modest level of reactivity and can undergo conversion to xanthine oxidase (XO). The synthesis of uric acid is mostly contingent upon the quantity of substrate available and the enzymatic activity of xanthine oxidase (XO). Ultimately, XDH/XO facilitates the concluding stages of purine metabolism, whereby hypoxanthine is converted into xanthine and xanthine is further transformed into uric acid (UA)(15,16)
The regulation of blood uric acid levels is heavily influenced by the kidney. The glomeruli have the capacity to efficiently filter the circulating uric acid within the renal tubule.

Approximately 90% of the filtered uric acid is reabsorbed via the proximal convoluted tubule's central region, primarily facilitated by the urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9) (17), Meanwhile, the remaining 10% is eliminated and constitutes around 60-70% of the total uric acid excretion in the body (18,19). In persons who are in a state of good health, the production and elimination of uric acid often remain relatively constant. Variations in the concentration of uric acid in bodily fluids can provide valuable insights on the functionality of the immune system, metabolism, and other physiological systems. If the human body produces an excessive amount of uric acid or if the excretion process is impaired, it may result in the accumulation of uric acid within the body. Hyperuricemia is defined as having a circulating uric acid level over 5.7 mg/dl for women and 7.0 mg/dl for males (20). Metabolic disease can occur when blood uric acid concentrations surpass normal levels, leading to the acidification of physiological fluids. This acidification hampers the normal functioning of human cells, ultimately impeding their capacity to perform optimally (21,22).

The concentration of uric acid may be subject to modulation by alterations in plasma glucose levels and insulin concentration (16).

Material and Methods

The study was approved by Internal Ethical of Sai Pg College & the consent were taken from all the participants, whereas all the standard guidelines & regulations were followed.

Exclusion Criteria

Subject with the following feature were not including in this study

- Consuming hypoglycaemic drugs
- On Insulin
- History of serious liver or kidney Disease
- History of stress.
- Consuming uricosuric agents
- Pregnant women
- Lactating women

Inclusion criteria

- Known Diabetic Patients.
- Subject having impaired fasting/postprandial glucose value.
- Subject with impaired HbA1c value.
- Subjects with above criteria falling in age groups (25-55) year and both sex.

The 5 ml overnight fasting blood samples was collected in Fluoride, EDTA & Plain vial by venepuncture and all the sample analysed in Biochemistry labs, for Blood Sugar parameters like, Fasting Blood Glucose & HbA1c, were divide in three group on the basis of guideline of American Association society of diabetes in Group I the value of HbA1c less (<) than 5.5 % and FBG is below 110 mg/dl , For group II the value considered between 5.5 - 6.6 % for HbA1c and value of FBG should be between 110 - 125 mg/dl ,Whereas for Group II HbA1c value is above 6.6% (> 6.6) and the fasting blood glucose is more than 125 mg/dl (>125) .

The enzymatic assays for HbA1c was used, whereas the GOD & POD method was used for estimations of FBS/PPBS by the colorimetric methods with the semi-auto analyser(Erba cm5) and Uric Acid estimation done by Uricase Enzymatic method.Thetests were conducted according to standard manufacturer protocol & precision of the measurement was maintained by regular method calibration with the reference standard.

Statistical analysis: Qualitative data were represented in the form of frequency and percentages. SPSS Version 22 was used for the statistical analysis.

Result

This study has included both the sexes of age group 25-55 years, the study was conducted on random people having general health random check-up. The total number of samples collected was 250. these samples were distributed in different groups on the basis of value of FBS & HbA1c into three Group I Normoglycaemic(n=85), Group II Pre- Diabetic(n=67) & Group III Diabetic (n=98) that is Group I, II, III as shown in Table 1.1.

Variable	No of Sample	FBS (mg/dl)	PPBS (mg/dl)
Group I	85	91.1±9.6	132.3±9.2
Group II	67	112.6±8.9	144.3±10.5
Group III	98	136.4±12.2	157.7±8.3

Table 1.1: Showing blood glucose level in three groups

Table 1.1 Shows the Blood Sugar Parameter analysis in Group I, Group II, Group III in which the level of FBS , PPBS were found to be raised in Group III , Moderate in Group II, and low in Group I

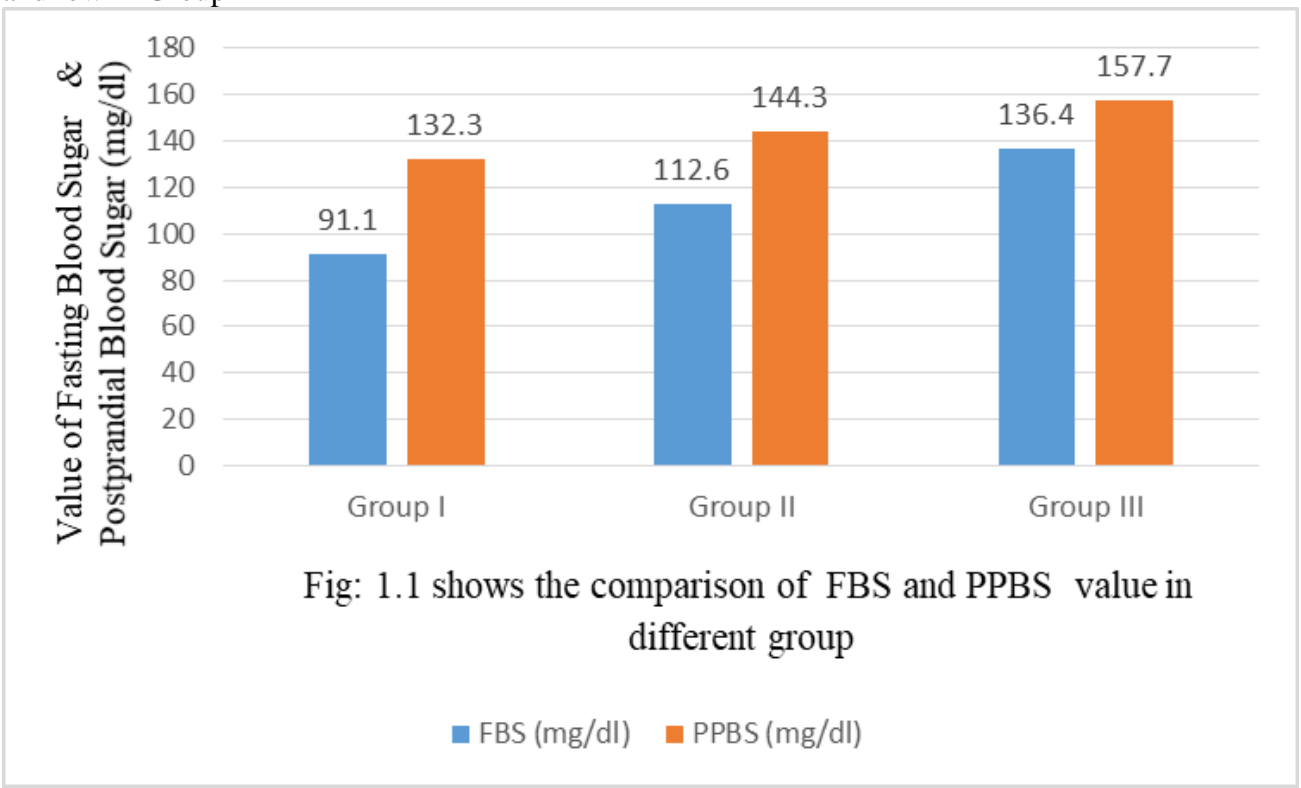

Fig: 1.1 shows the comparison of FBS and PPBS value in different group

Fig: 1.1 Shows the level of Blood Sugar Parameter analysis in Group I, Group II, and Group III

Variable	No. of Sample	Uric acid(mg/dl)	HbA1c (%)
Group I	85	4.2±0.7	5.3±0.2
Group II	67	7.1±1.0	6.1±0.2
Group III	98	5.5±0.6	7.1±0.3

Table 1.2: Showing the level of HBA1c and in URIC ACID in Group I, Group II, and GroupIII.

Table 1.2 also shows the Blood Sugar Parameter analysis Along with Uric acid comparison in Group I, Group II, Group III in which the level of uric acid & HbA1C were found to be

raised in Group III, Moderate in Group II, and low in Group I whereas Uric Acid level were moderately increases in Group III & Highly increased in Group II & least in Group I

Fig: 1.2 Shows the level of uric acid in different groups

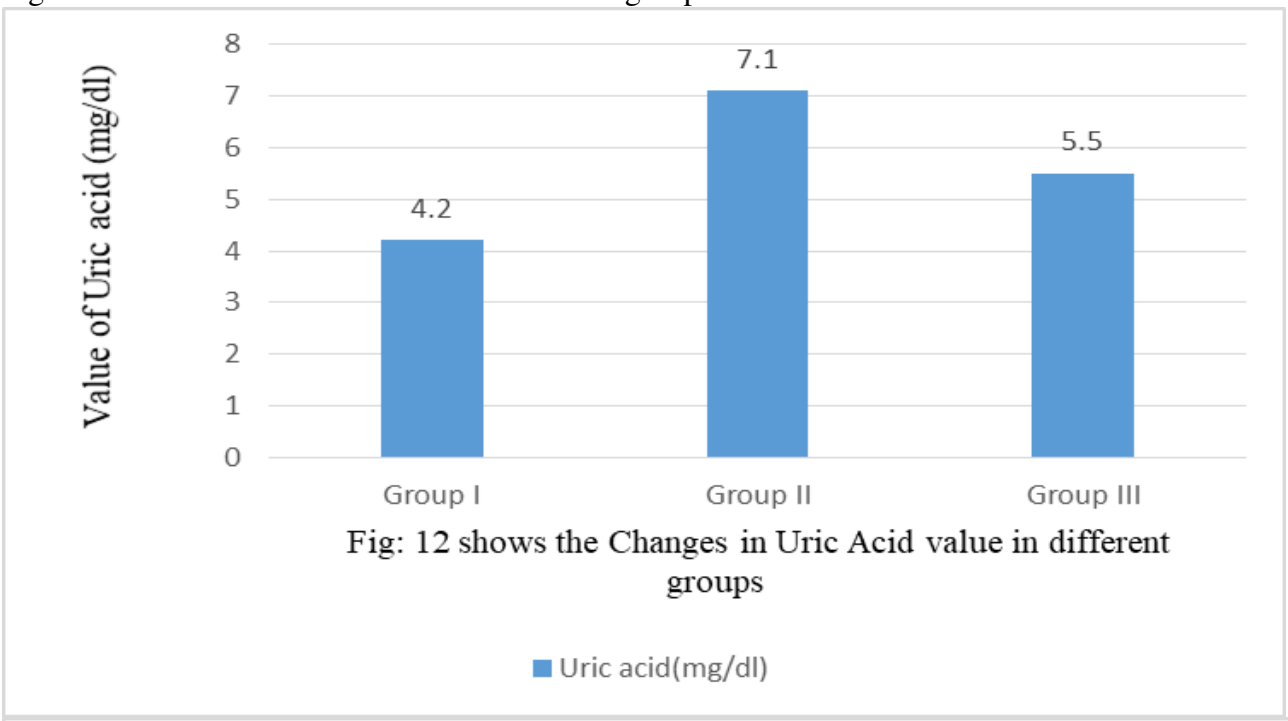

Fig: 12 shows the Changes in Uric Acid value in different groups

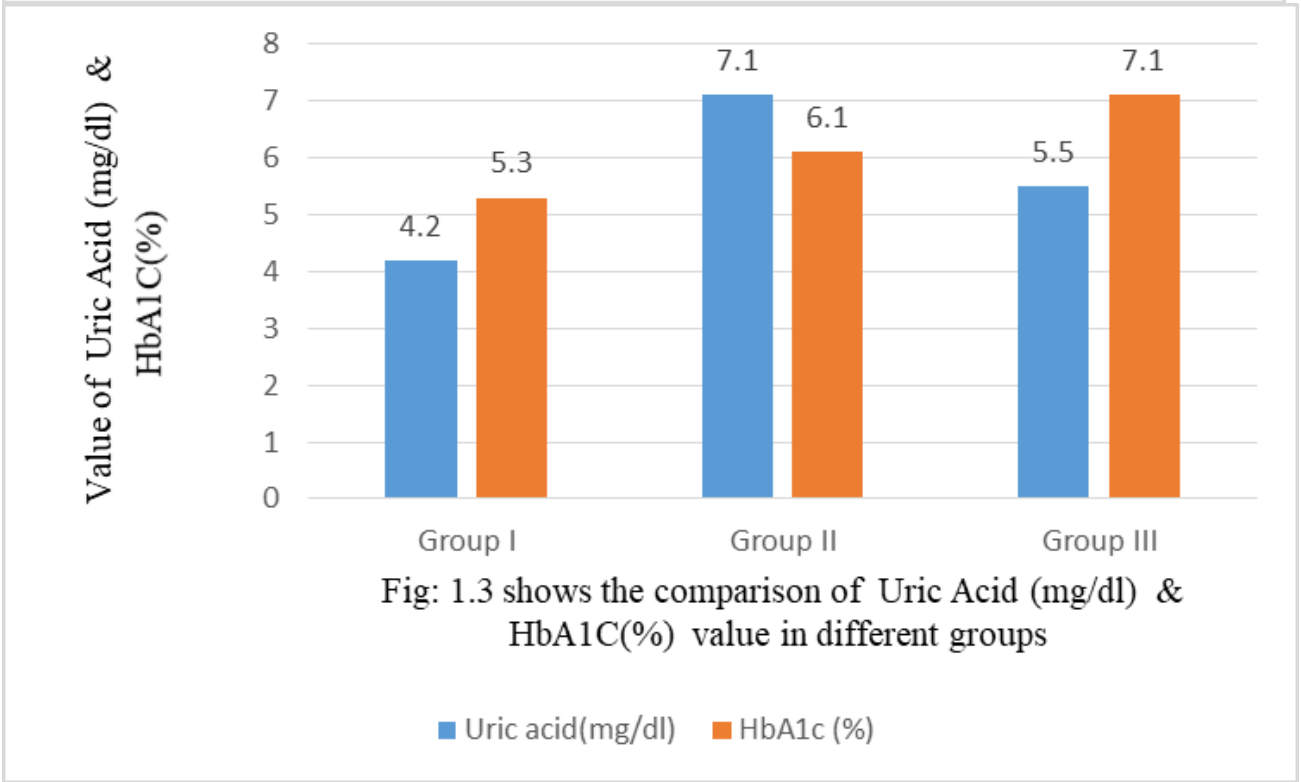

Fig: 1.3 shows the comparison of Uric Acid (mg/dl) & HbA1C(%) value in different groups

FIG: 1.3 Shows the comparison of s uric acid and HBAIC level in three different groups

Groups	***t* test**	**SIGNIFICANCE**
Group I & Groups II	21.560	Statistically Significant
Group II & Groups III	13.155	Statistically Significant
Group I & Groups III	13.967	Statistically Significant

Table 1.4 Significance value of uric acid in different groups

Table 1.4 Showed the significant difference in the level of S.Uric acid in all the three groups.

Discussion:-

Our findings indicate that Group II showed the highest level of uric acid when compared to the other two groups. When analysing the blood sugar parameter (FBS, PPBS and HbA1C) along with uric acid ,we observed a positive correlated between Group I and Group II, while a negative correlation was observed between Group II and Group III,

In line with previous research, our study revealed that individuals with diabetes exhibit noticeably reduce levels of serum uric acid compared to those who are pre-diabetic. This aligns with the findings of previous studies, which indicated that pre- diabetic individuals tend to have higher levels of uric acid than their healthy counterparts (23).

The uricosuric effect of glycosuria may explain the low uric acid concentration among diabetic patients with severe hyperglycemia. Changes in plasma glucose and insulin concentrations may also influence uric acid levels (24). Uric acid variations in prediabetes and diabetes have traditionally been viewed as a secondary metabolic event (25,26)then rise again after renal insufficiency (27).

A study on the relationship between Haemoglobin A1c, fasting glucose with serum uric acid levels found that serum uric acid causes insulin resistance, hyperuricemia frequency increased with moderately increasing levels of HbA1c and FPG, but decreased with higher levels of HbA1c (28). The bell-shaped relationship between blood glucose and serum uric acid levels may be related to the uricosuric effect of glycosuria (29).

Pre-diabetes is distinguished by impaired glucose tolerance and insulin resistance, albeit to a lesser extent than full-blown diabetes. In the early phases of insulin resistance, compensatory hyperinsulinemia occurs, which can result in increased uric acid synthesis and decreased renal excretion of uric acid (30).

People with pre-diabetes frequently have central obesity and metabolic abnormalities, which lead to elevated uric acid levels. Visceral adipose tissue is metabolically active and produces inflammatory cytokines, which contribute to insulin resistance and hyperuricemia (31).

Earlier studies also reported similar findings, reported the positive association between Hyperuricemia and prediabetes [32,33,34].

The variability in uric acid concentrations can serve as an autonomous indicator of pre-diabetic states, potentially leading to the development of diabetes as a subsequent metabolic event. A reduction in both basal and glucose-induced insulin production has been seen in vitro conditions using isolated pancreatic islets in cases of hyperuricemia (35, 18).

The evidence was also replicated using a meta-analysis, which indicated that an increase of one mg/dl in uric acid levels is associated with a 17% increase in the probability of

developing type 2 diabetes mellitus (T2DM) .Oxidative stress has been found to impede the manufacturing of adiponectin, as well as hinder the functioning of pancreatic beta cells (10,36).

The presence of hyperuricemia in individuals with pre-diabetes has been observed to impede the renal excretion of uric acid. It has been found that insulin has the ability to stimulate the urate-anion co-transporter located in the brush border of the proximal renal tubule, hence facilitating the reabsorption of urate in the kidneys. This mechanism provides an alternative pathway for renal urate reabsorption (37).

A significant association has been observed between purine metabolic disease, such as gout, and insulin resistance, leading to the development of type 2 diabetes. Several previous studies and meta-analyses have consistently demonstrated a substantial correlation between hyperuricemia and an elevated risk of type 2 diabetes mellitus (T2DM) (38)

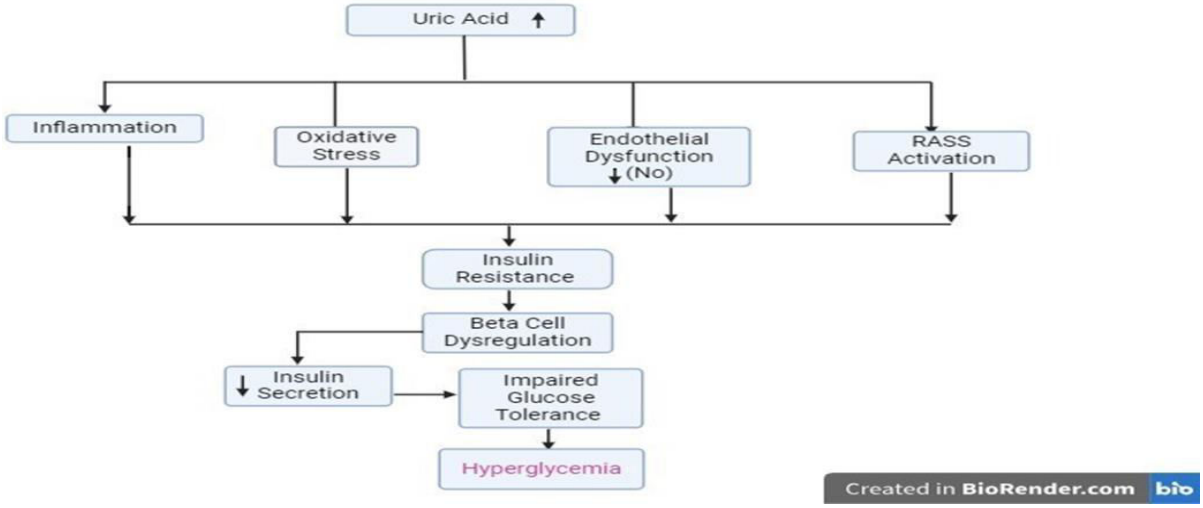

Fig:1.4 Association between Uric Acid and hyperglycaemia

The generation of uric acid is associated with both mitochondrial oxidative stress and inhibition of AMP-activated protein kinase (AMPK), which is responsible for causing many of the effects of fructose leading to induced metabolic syndrome. Previous studies have confirmed that uric acid has the capacity to inhibit AMP-activated protein kinase (AMPK) and promote gluconeogenesis (38, 39). Uric acid induces oxidative stress in adipose tissue cells, leading to a reduction in the synthesis of adiponectin (40). Elevated levels of urate transporters have been observed in the pancreatic islets of rats afflicted with diabetes, and it has been demonstrated that uric acid induces oxidative stress in these islet cells (41). The plasma concentration of insulin did not exhibit any correlation with the initial increase in serum uric acid levels, indicating that uric acid functions as an autonomous risk factor in the progression of insulin resistance and later development of diabetes.

Furthermore, factors that are linked to the likelihood of developing type 2 diabetes mellitus (T2DM) include age, race, and familial history of the disease, body mass index (BMI), glucose intolerance, and metabolic syndrome (Met S). However, there have also been proposals for SUA levels. Numerous investigations have provided evidence of an association between serum uric acid (SUA) levels and insulin resistance, leading to the proposition that uric acid (UA) plays a substantial role in the progression of insulin resistance (42,43).

Because uric acid is linked to the development of diabetes mellitus and related disorders, its importance has been recognised more and more. Given the rising prevalence of diabetes, it is imperative to investigate the effects of hyperuricemia in patients with type 2 diabetes (44).

Conclusion

The trends showed high uric acid in Pre-Diabetes followed by Diabetes & Non -Diabetes people. The Blood sugar parameters wereanalysed and Serum UA has an important relationship with HbA1c levels in the diagnosis, not only in Pre-Diabetic conditions but can be helpful as diagnostic marker Type 2 Diabetes. Serum Uric acid first increased with increase in fasting blood glucose, originally serum uric acid increased. Along with hyperglycaemia due to many factors such hyperinsulinemia, paradoxical urate redox shuttle, production of xanthine oxidase, whereas serum uric acid drop in progressive hyperglycaemia can be attributed to glycosuria generating uricosuria and decrease in salt reabsorption.The level of uric acid can direct glucose metabolism worsening rather than advanced insulin resistance measurements, should be checked on a regular basis to aid in the early detection and prevention of Type 2 diabetes and its consequences.

Recommendation

The pre-diabetic profile is limited in scope and provides a narrow diagnostic spectrum. However, including the uric acid test into this profile not only broadens the diagnostic options, but also allows for a more exact examination of the patient's health record. This can benefit in diabetes prevention by motivating lifestyle modifications that are more cost-effective, particularly for persons with lower socioeconomic status.

Declarations:

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

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors' contributions: Author equally contributed the work.

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