"SERUM URIC ACID AND HbA1C CORRELATION IN PREDIABETIC AND DIABETIC PATIENTS- A ONE YEAR PROSPECTIVE ANALYTICAL STUDY AT KLE'S DR PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTER"

BY

REG NO. BG0119012

Dissertation

Submitted to the
KLE Academy of Higher Education and Research,
Belagavi, Karnataka.

In partial fulfillment
of the requirements for the degree of

DOCTOR OF MEDICINE
IN
GENERAL MEDICINE

JAWAHARLAL NEHRU MEDICAL COLLEGE
BELAGAVI- 590010. KARNATAKA

APRIL-2021

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH,

BELAGAVI, KARNATAKA

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LIST OF ABBREVIATIONS USED

T2DM	Type 2 Diabetes Mellitus
DM	Diabetes Mellitus
IDF	International Diabetes Federation
IR	Insulin Resistance
β cell	Beta cell
SUA	Serum Uric acid
UA	Uric acid
HTN	Hypertension
BMI	Body Mass Index
ADA	American Diabetes Association
MODY	Maturity Onset Diabetes of the Young
Log	Logarithm
FBS/FPG	Fasting Blood Sugar / Fasting Plasma Glucose
RIA	Radioimmunoassay
OGTT	Oral Glucose Tolerance Test
&	And
kg	Kilogram
h	Hour
A1C	HbA1c
G6PD	Glucose 6 Phosphate Dehydrogenase
HIV	Human Immunodeficiency Virus
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
HDL	High Density Lipoprotein

GDM	Gestational Diabetes Mellitus
BP	Blood Pressure
kg	Kilogram
EGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiography
RBC	Red Blood Cells
OHAs	Oral Hypoglycaemic Agents
T1DM	Type 1 Diabetes Mellitus
LADA	Latent Autoimmune Diabetes in Adults
URAT1	Urate Transporter 1
GLUT9	Glucose Transporter Type 9
OAT	Organic Anion Transporter
ABCG2	ATP-binding cassette super-family G member 2
HPRT	Hypoxanthine-Guanine Phosphoribosyltransferase
PRPP	Phosphoribosyl Diphosphate
eg	Example
etc	Et cetera
TG	Triglyceride
NO	Nitric Oxide
eNOS	Endothelial Nitric Oxide Synthase
O_2^-	Superoxide
XO	Xanthine Oxide
$ONOO^-$	Peroxynitrite
dl	Deciliter
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells

iNOS	Inducible Nitric Oxide Synthase
ROS	Reactive Oxygen Species
AMPK	Adenosine Monophosphate – activated Protein Kinase
ERK	Extracellular signal Regulated Kinase
Dept	Department
HbA1C	Glycosylated Haemoglobin
ml	Mililiter
SPSS	Statistical Package for the Social Sciences
SD	Standard Deviation
χ^2	Chi Square
R^2	Coefficient of determination
%	Percentage
kg/m^2	Kilogram per meter square

ABSTRACT

Diabetes is due to deficiency in insulin production, insulin action, or both and is a metabolic syndrome defined by hyperglycemia. Uric acid and HbA1c levels were examined in this study to see if there was any correlation.

At KLES Dr Prabhakar Kore Hospital and Research centre, the department of General Medicine conducted this investigation. People between the ages of 30 and 70 who were diagnosed with Type 2 Diabetes Mellitus and Prediabetes were included in this research. Patients with Myeloproliferative or Lymphoproliferative illnesses, psoriasis, pregnancy, gout and on treatment with medications for gout and alcoholics were excluded. The enzymatic approach was used to measure serum uric acid (UA) using an automated device, and the HPLC technique was used to measure whole blood HbA1c.

Results: After acquiring informed consent, a total of 108 patients were included in the research. Of the 108 individuals, 67 had diabetes and 41 had pre-diabetes. There was a male majority among this study's participants, with a mean age of 59.12±14.06years. The serum uric acid was substantially greater among the patients with diabetes mellitus (6.76±3.1mg/dL) compared to participants with pre-diabetes (5.5±1.9mg/dL). The serum HbA1c and the serum uric acid have a mild positive significant association in diabetics. Conclusion: There is a very weak association of serum uric acid with HbA1c among the diabetic patients. Diabetes mellitus patients have greater blood uric acid levels than those with pre-diabetes mellitus.

Keyword: Diabetes mellitus, Pre-diabetes, HbA1c, Serum Uric acid.

TABLE OF CONTENTS

LIST OF TABLE

LIST OF FIGURES

INTRODUCTION

Diabetes mellitus is a group of diseases characterised by hyperglycemia brought on by either insulin production or insulin action, or both. Type-1 and type-2 are the two main subtypes that it falls under. Type-1 diabetes mellitus is characterised by a severe or near-severe lack of insulin. In type-2 diabetes mellitus there is diminished capacity of the insulin to act on the peripheral tissue, which is called insulin resistance. It is possible for the pancreas cells to generate enough insulin in the early stages of insulin resistance in order to control blood glucose levels. Type-2 diabetes can occur from the failure of cells caused by insulin overproduction. Chronic hyperglycemia is related with long term damage, malfunction and failure of multiple organs including eyes, kidneys, nerves and heart. [(1)]Poor glucose tolerance or low fasting glucose levels characterise the condition known as prediabetes, a disorder of glucose homeostasis. It is possible to reverse both intermediate hyperglycemic stages, but the risk of acquiring type 2 diabetes is increased. [(1)] The prevalence of diabetes mellitus is rising at an alarming rate over the world and is on its way to pandemic proportions. People (aged 20–79) with diabetes account for 6.4% of the global population in 2010, rising to 406 million adults in 2018 and 511 million adults in 2030, according to the World Diabetes Atlas. India has the greatest number of diabetes patients in the world projected to be roughly 69.2 million in the year 2015 and anticipated to climb to approximately 87 million by the year 2030. [(2)] Wild et al have anticipated a similar two fold escalation in the prevalence of diabetes in the globe as a whole, with a highest increase in India impacting up to 79.4 million persons. [(3)] Hence diabetes is a serious health care concern in India.

Renal damage may be accurately predicted by both diabetic and non-diabetic patients using the blood uric acid level.

[4] The last breakdown result of purine metabolism is uric acid, which is created by xanthine oxidase's enzymatic activity[5]

HbA1c is a commonly accessible test which is typically indicated by most doctors to assess the long term glycemic control in diabetes patients over the duration of prior 2-3 months. Glycated haemoglobin (HbA1c) is an established marker of the mean blood glucose and the indication of the glycemic management in the diabetic persons. A1c in haemoglobin binds non-enzymatically to circulating glucose, resulting in the measurement. HbA1c levels will rise as a result of increased glucose levels in the bloodstream.[6] HbA1c is also a biomarker of risk factors for diabetic micro- and macro-vascular problems and provides information on the degree of hyperglycemia.

Individuals with diabetes mellitus or prediabetes in India are at a significant disadvantage due to a dearth of research on the association between serum uric acid and glycemic control (HbA1c). As a result, this research looked at the relationship between uric acid and HbA1c levels.

AIM AND OBJECTIVE

Aim

To study the correlation between serum uric acid and HbA1c in people with prediabetes and type 2 diabetes.

Objective:

- To evaluate the blood uric acid levels and HbA1c levels of individuals with type 2 diabetes mellitus and prediabetes.
- To correlate the relationship between serum uric acid levels and HbA1c in people with type 2 diabetes and those who are pre-diabetic.

REVIEW OF LITERATURE

Diabetes mellitus - an overview

Hyperglycemia resulting from abnormalities in insulin production, insulin action, or both is the feature of diabetes mellitus, a group of metabolic diseases. Diagnosing diabetes mellitus is recommended by the American Diabetes Association Expert Panel if any one of the three criteria have been met. (7) Diabetes is a worldwide epidemic. Diabetes prevalence has grown internationally as a result of changing lifestyles and growing obesity. In 2017, 425 million people throughout the world were living with diabetes. As of 2015, around 10% of the American population was diagnosed with diabetes, according to the IDF. an total of 7 million of these patients were left untreated . The prevalence of diabetes climbs as people get older. Diabetes affects roughly 25 percent of the population over the age of 65.(8)

Criteria for the diagnosis of Diabetes Mellitus(7)

1) Symptoms of diabetes plus casual plasma glucose concentration > 200 mg/dl.

The term ‘‘casual’’ refers to attire that can be worn at any time of day or night, regardless of when one last ate. Polyuria, polydipsia, and unexplained weight loss are all classic signs of diabetes.

2) Glucose in the bloodstream ≥126 mg/dl. Fasting is defined as a period of at least eight hours of no food intake.

3) During an oral glucose tolerance test, 2 hours of plasma glucose ≥ 200 mg/dl.

DIABETES MELLITUS CLASSIFICATION

Under the new classification, there are four types of diabetes mellitus. There are three forms of diabetes: type 1, type 2, and gestational (9).

Type 1 diabetes (formerly known as IDDM or Juvenile Onset Diabetes) is defined by the death of β-cells as a result of an autoimmune process, resulting in absolute insulin deprivation.

Type 2 (NIDDM / Adult onset) is characterized by insulin resistance in peripheral tissues as well as a lack in cell insulin secretion.

Other Specific Types: People with hereditary difficulties with cell function (MODY, or Maturity-onset Diabetes Mellitus) or insulin action fall into this group. People with disorders of the exocrine pancreas or endocrinopathies who have exocrine pancreatic malfunction.

Pathophysiology

T2DM is an insulin-resistance condition followed by beta-cell dysfunction. Initially, there is a compensatory increase in insulin production, which keeps glucose levels within normal ranges. Hyperglycemia occurs when insulin production is inadequate to maintain glucose homeostasis when beta cells shift as the illness progresses. The majority of T2DM patients are obese or have a higher body fat percentage, with the bulk of it concentrated in the abdominal region. Insulin resistance is caused by a number of inflammatory events in adipose tissue, such increased FFA release and adipokine dysregulation.

People with hypertension or dyslipidemia who had GDM in the past are more likely to acquire T2DM, as is a lack of physical exercise. Adipokine dysregulation, inflammation, altered incretin biology with diminished incretins such as glucagon-like

peptide-1 (GLP-I) or incretin resistance, hyperglucagonemia, increased renal glucose reabsorption, and gut microbiota abnormalities all play a part.

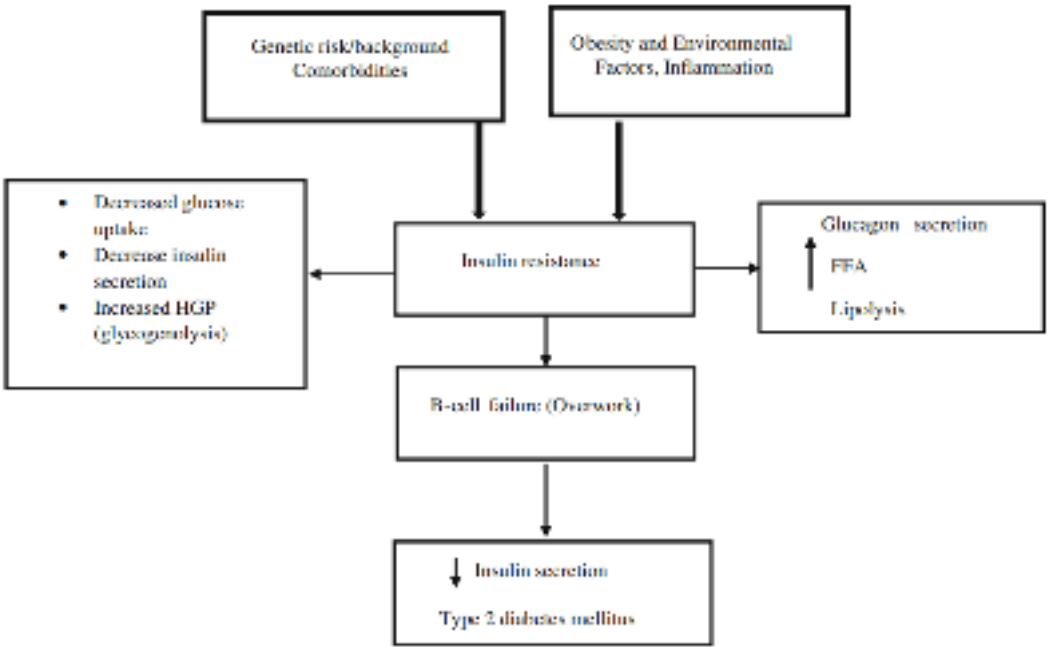

Figure 1: Mechanism of genetic predisposition and obesity induced insulin resistance and T2DM

The glucose transporter 2, which is mostly mediated by the glucose transporter 2, is required for insulin release by beta cells. (GLUT-2). Glucose intolerance was developed in mice with a genetic change affecting GLUT-2 expression; similar changes in GLUT-2 were found in normal mice fed a high-fat diet, suggesting a possible mechanism for the link between high-fat diet and diabetes development.

T2DM is characterised by

- Reduced glucose absorption due to insulin resistance in the muscle
- insulin resistance in the liver, which results in a rise in blood glucose levels
- Increase in plasma free fatty acids due to adipocyte insulin resistance
- Increased insulin resistance promotes the adipocytokine release
- Beta-cell degeneration with time

- Hyperglucagonemia
- Decreased incretin activity (GLP-1 and GIP)
- Increased glucagon sensitivity in the hepatic
- Renal glucose reabsorption is now higher than before.
- Brain neurotransmitter malfunction leading to failure of appetite reduction resulting in weight gain

Risk factors

- Obesity
- The distribution of fat
- Inactivity
- Your family's history
- Race and ethnicity
- Hypertension
- Dyslipidemia
- Getting older
- Pre-diabetes
- Risks associated with pregnancy (history of GDM)
- Insulin resistance, which is caused by an incompletely understood reduction in insulin function, is the most commonly recognized and unifying explanation for the pathophysiology of the metabolic syndrome. Insulin resistance begins with postprandial hyperinsulinemia, then fasting hyperinsulinemia, and finally hyperglycemia.

Table 1: Major causes for insulin resistance
Inherited states of target cell resistance
Leprechaunism (insulin-receptor mutations)
Rabson-Mendenhall syndrome (insulin-receptor mutations)
Type A syndrome of insulin resistance (insulin-receptor mutations in some, unknown signaling defect in most)
Some lipodystrophies
Secondary insulin resistance
Obesity (free fatty acids and adipocytokines may contribute)
Stress, infection due to excess counterregulatory hormones (cortisol, catecholamines, growth hormone, glucagon)
Medications (eg, glucocorticoids, HIV antiretrovirals, oral contraceptives)
Inactivity
Pregnancy (placental lactogen)
Immune mediated (anti-insulin antibodies, anti-insulin receptor antibodies in type B syndrome)
Miscellaneous (starvation, uremia, cirrhosis, ketoacidosis)
Consequences of insulin resistance
Most cases of type 2 diabetes mellitus
Cardiovascular disease, hypertension
Polycystic ovary syndrome
Metabolic syndrome
Obesity-related cancers

- An excess of circulating fatty acids is a crucial early factor to the formation of insulin resistance (Fig. 422-2).Triglyceride reserves generated by intracellular lipolytic enzymes in adipose tissue are the primary source of plasma albumin-bound free fatty acids. Lipoprotein lipase, which catalyzes the lipolysis of triglyceride-rich lipoproteins in tissues, also produces fatty acids. Insulin is implicated in both antilipolysis and lipoprotein lipase activation in adipose tissue. In addition to lowering insulin's antilipolytic impact, greater lipolysis that occurs in response to insulin resistance also releases more fatty acids into the bloodstream. Excess fatty acids increase substrate availability while also causing insulin resistance by altering signalling downstream. In both skeletal and cardiac muscle, fatty acids obstruct insulin-mediated glucose absorption and accumulate as triglycerides, whereas the liver increases glucose production and triglyceride accumulation.
- The metabolic syndrome may be caused by leptin resistance. Leptin lowers appetite, increases calorie intake, and improves insulin sensitivity. Furthermore, leptin can alter cardiac and vascular function via a nitric oxide–dependent mechanism. Instead, obesity leads to hyperleptinemia, which leads to inflammation, insulin resistance, high cholesterol, and a slew of cardiovascular diseases such as coronary heart disease (CHD), atherosclerosis (a disease of the arteries), hypertension (high blood pressure), and heart failure (low blood pressure) (low blood pressure).
- Oxidative stress is one notion that helps explain why people age and develop metabolic syndrome. A deficit in mitochondrial oxidative phosphorylation that leads to the development of triglycerides and associated lipid molecules in muscle

has been discovered in research of insulin resistant adults with obesity or type 2 diabetes, the offspring of type 2 diabetes patients, and the elderly.

Uric acid

Uric acid is generated both exogenously and endogenously. SUA levels in the body are substantially regulated by renal and gastrointestinal production and excretion. Purine generation and degradation are helped by a range of enzymes. Urates are the most frequent ionised form of uric acid in ECF and synovial fluid, accounting for 96 percent of the total at pH 7.4. In uric acid, a substance's solubility in urine is determined by its pH. Purine is present predominantly in organs that contain xanthine oxidase enzymes, such as the liver and the gut. Urate production is not altered by an individual's purine intake or the salvage of purine synthesis and metabolism. Urate is largely eliminated by the kidney, with the remainder going through the colon. Purine metabolism abnormalities can induce hyperuricemia owing to urate overproduction, although these are relatively rare in the population when compared to a number of medical diseases, medicines, and other factors that can also cause increased purine biosynthesis or urate production.

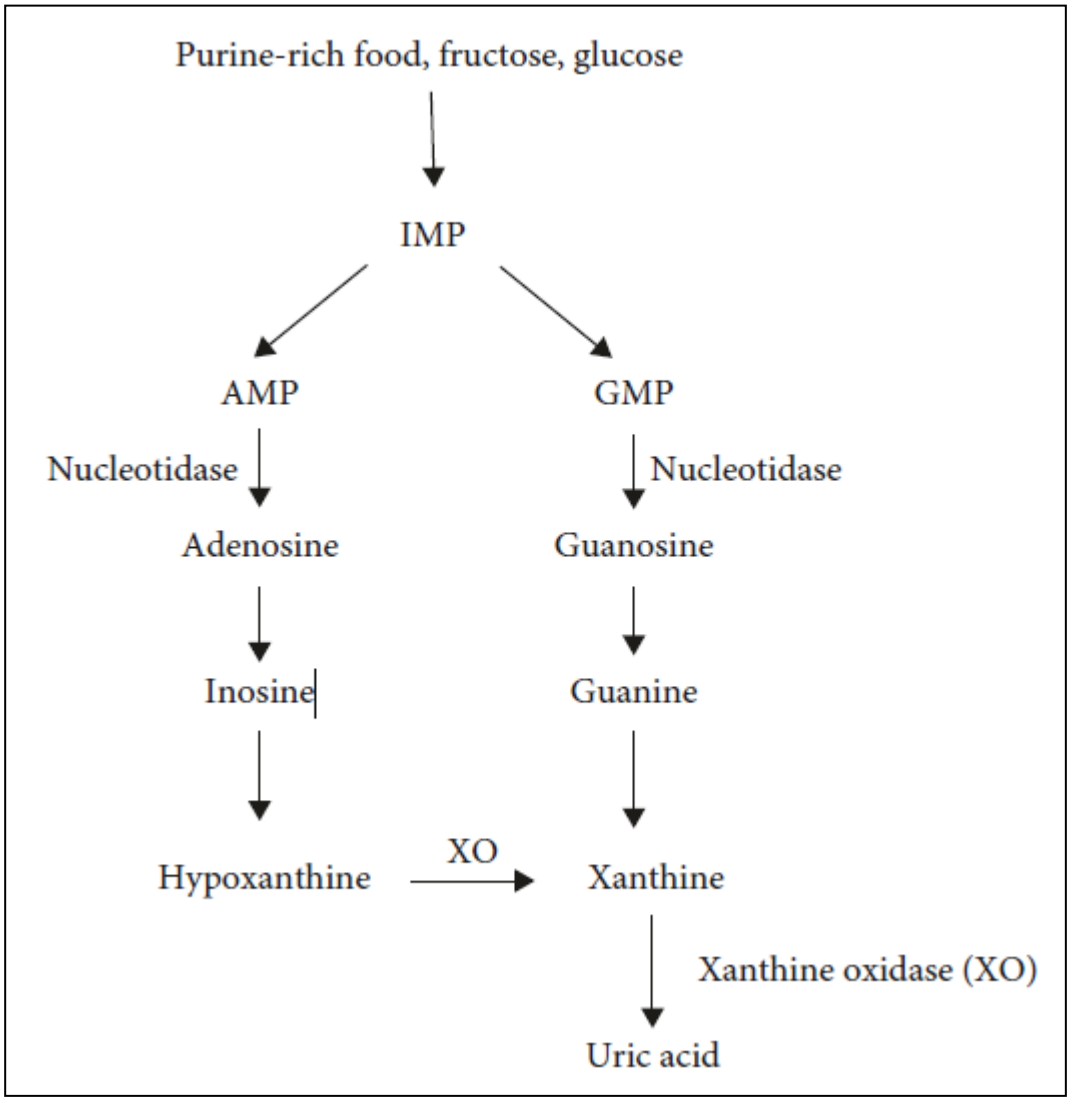

Figure 2: Process of purine metabolism in humans

Table 2: Hyperuricemia can be caused by an increase in purine biosynthesis and/or urate production.

Inherited enzyme defects leading to purine overproduction (rare monogenic disorders)
Hypoxanthine-guanine phosphoribosyl transferase deficiency
Phosphoribosyl pyrophosphate synthetase over activity
Glucose-6-phosphatase deficiency (glycogen storage disease, type I)
Clinical disorders leading to purine and/or urate overproduction
Myeloproliferative disorders
Lymphoproliferative disorders
Malignancies
Hemolytic disorders
Psoriasis
Obesity
Tissue hypoxia
Down syndrome
Glycogen storage diseases (types III, V, VII)
Drug-, diet-, or toxin-induced purine and/or urate overproduction
Ethanol
Excessive dietary purine ingestion
Pancreatic extract
Fructose
Vitamin B12 deficiency
Ethylamino-1,3,4-thiadiazole
4-amino-5-imidazole carboxamide riboside
Cytotoxic drugs

Pathological mechanism of uric acid and diabetes

Many recent investigations have demonstrated a pathogenic mechanism pertinent to

• Inflammation

• Oxidative stress

• Endothelial malfunction

• Inhibiting insulin pathway

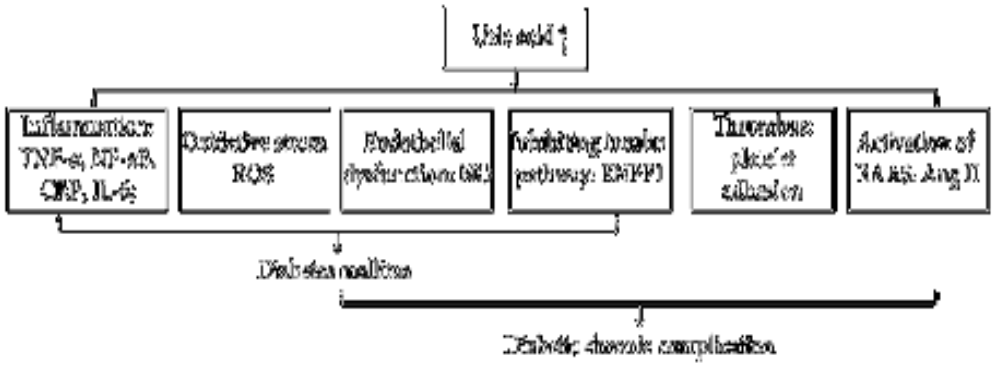

Figure 3: Metabolism of uric acid leading to diabetes mellitus

Inflammation: Elevated uric acid levels in the blood stimulate the expression of interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and CRP production. In clinical experiments, UA-induced inflammation lowers insulin sensitivity in mice, and UA infusion can boost TNF- levels and activate the classical inflammatory pathway. Serum UA was discovered to be related with TNF-, interleukin-6, and C-reactive protein in healthy persons in human investigations. (10–12)

Oxidative stress: Excess uric acid produces an increase in reactive oxygen species (ROS) production, which promotes inflammation and vascular dysfunction. UA is a powerful antioxidant capable of eliminating superoxide and hydroxyl radicals from plasma, and it has pro-oxidant characteristics in vascular tissue by enhancing ROS production, such as ROS. UA-mediated oxidative stress-induced lipid peroxidation, DNA damage, and inflammatory factor activation finally result in cellular damage. Oxidative stress can also alter insulin gene expression, resulting in a decrease in insulin secretion. (13)

Endothelial dysfunction is defined by reduced endothelial-derived NO production and/or bioavailability. Moreover, UA lowers endothelial NO bioavailability in humans. Endothelial cell growth and migration, as well as NO secretion, are inhibited by uric acid. UA can combine with NO to generate 6-aminouracil, UA-dependent ROS can react with NO to form peroxynitrite, and UA

can both impede and increase L-arginine absorption. Because of the effects of hyperglycemia and neuro-hormonal stimulation, UA levels are independently linked to endothelial dysfunction in animals and people, elevating hypertension. (15–18)

Review of articles

Uric acid (UA) is a key focus of the research, since it is an oxidative marker as well as a marker for endothelial damage, cardiovascular disease, and renal injury. Uric acid is created when adenosine and guanine (purines) are broken down by hypoxanthine, which is then converted to xanthine and then to uric acid by Xanthine oxidase. Xanthine Oxase produces toxic oxidants during purine breakdown, which may have a role in cardiovascular disease, endothelial damage, and renal failure. (19) The colon digests one-third of the uric acid, while the kidneys remove the other two-thirds. Because uric acid produces oxygen free radicals (ROS), this might be a simple and useful clinical marker for excessive oxidative stress, which causes damage to the endothelium and microvasculature. Glycated haemoglobin (HbA1c) is a widely established marker of glycemic management in diabetics and a measure of mean blood glucose levels. The non-enzymatic binding of circulatory glucose (carbohydrate in main fraction) N-terminal valine to haemoglobin -chain occurs in prolonged hyperglycemia, resulting in dominant glycated haemoglobin, such as HbA1c. The binding is directly related to blood glucose levels. As a result, higher HbA1c values indicate a person's overall blood glucose level. (21) Another research in Japanese patients with normal renal function (22) indicated that higher uric acid levels (>7mg/dL) were related with a 2.9fold greater chance of having renal insufficiency within 2 years in males and a 10 times higher risk of developing renal insufficiency within 2 years in women. (23)

In a developed animal model, researchers nourished oxonic acid (a uricase inhibitor) to induce hyperuricemia and acute renal failure, elucidating the link between chronic hyperuricemia and renal injuries, most likely through a mechanism involving increased juxtaglomerular rennin and decreased macula densa neuronal nitric oxide synthesis (NOS).(24)

In addition to the aforementioned mechanism, mild hyperuricemia causes glomerular hypertension and thickening of the renal afferent arteriolar walls, which promotes the progression of renal disease.

(25) Elevated uric acid levels connect with the development of the renal insufficiency in the persons with the normal kidney function. Ohta Y et al., have observed that higher uric acid level enhanced the renal function loss in patients with hypertension throughout the 10-year of observational research. (26) Another study discovered that a greater blood uric acid level was linked to a lower glomerular filtration rate (GFR) as evaluated by serum Cystatin C. (27) Another research found that people with diabetes mellitus have a lower urine albumin excretion rate, adding to the evidence of a link between high serum uric acid and DN.(28)

Previous studies have revealed a beneficial link between the blood uric acid levels and HbA1c management in the diabetes and Prediabetes patients. Haque T et al. conducted a prospective study in 300 individuals to look into the link between blood uric acid and HbA1c levels in healthy, prediabetic, and diabetic people.They discovered that serum uric acid levels were high in healthy persons but fell with presence of diabetes and prediabetic patients with rise in HbA1c and FBS concentration. (29)

Dehghan A et al. established in a prospective population-based research to analyse blood uric acid as a noval risk factor for type-2 diabetes that there is a strong and independent risk factor for diabetes. (30)

Chien KL et al. conducted a cross-sectional study to look at plasma uric acid and the risk of type 2 diabetes in the general population. They discovered a small but significant link between plasma uric acid levels and the occurrence of type 2 diabetes. The presence of metabolic syndrome in the patients helped to moderate the link. (31)

Rabari K et al. conducted another observational study in 721 Indians to evaluate blood uric acid levels and their relationships with glycemic parameters in Prediabetes and diabetes mellitus patients. In north Indian cultures, blood uric acid was revealed to be a determinant of altered glucose metabolism but not a probable predictor of Prediabetes. (32)

In prospective study done by Rao SM et.al, to determine the blood uric acid level is diabetes mellitus and Prediabetes in a south Indian tertiary care hospital. Patients with diabetes mellitus had a lower serum uric acid level than those with pre-diabetes, while those with pre-diabetes had greater levels than those with normal blood sugar levels. This provides as possible indicator of worsening of glucose metabolism. (33) Similarly, Sachan P et al. conducted a cross-sectional observational study to explore the relationship between serum uric acid and Prediabetes in an Indian population. They hypothesised that blood uric acid levels were much higher in the Prediabetes group, and that this may play a key role in diabetes progression. (34)

In a research by George M et al., to examine the amount of blood uric acid in patients with diabetes mellitus. The study also offers support for the hyperuricemic impact of metformin and other hypoglycemic medications. BMI elevates the likelihood of having hyperuricemia, and hypertriglyceridemia is fairly high in

overweight, class 1,2,3 obese adults. Thus, the study may be summarised by stating that controlling BMI, uric acid, and triglyceride levels may lessen the proportion of diabetes complications. (35)

However, the impact of the serum uric acid level in prediabetic and diabetic patient is little researched in connection with the developing nation populations.

MATERIALS AND METHODS

Source of Data: KLES Dr. Prabhakar Kore Hospital and MRC, Belgaum

Study design: Prospective analytical observation type of study

Study Period: One year hospital based study

Study place: After obtaining informed consent from all participants who met the inclusion criteria, patients at the general medicine OPD and IPD were included in this study.

Sample size: The study included a total of 100 participants in the study, 60 of whom were diagnosed with diabetes and 40 of whom were diagnosed with pre-diabetes.

$$n \geq \frac{\left(Z_{1-\alpha/2} - Z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2/r\right)}{(\mu_1 - \mu_2)^2}$$

n-sample size

σ-standard deviation

μ-difference between means

α-error

β-error

Inclusion criteria: -

- Type 2 diabetics and those with prediabetes who are in the 30-70-year age.
- Diabetes mellitus criteria(36):
    - FBS: ≥126mg/dL.
    - 2h glucose tolerance: ≥200mg/dL.
    - HbA1c: >6.5%.

- Prediabetes mellitus criteria(36):
    - FBS: 100-125mg/dL.
    - 2h glucose tolerance: 140-200mg/dL.
    - HbA1c: 5.7%-6.4%.

Exclusion criteria:-

- Patients on medications for hyperuricemia
- Alcoholics.
- Myeloproliferative diseases.
- Lymphoproliferative diseases.
- Psoriasis.
- Pregnancy.
- Gout.

Mode of selection of cases:

ll patients matching the inclusion criteria and willing to participate were enrolled in the trial. The procedure was described to the patient, informed consent taken. Venous blood was obtained from each patient following an overnight fast and used for the biochemical analysis. Serum Uric acid (UA) was tested on automated device by enzymatic method and Whole blood HbA1c was assessed by HPLC technology.

STATISTICAL ANALYSIS

IBM SPSS version 23 was used to do statistical analysis on the data. The data was provided as a mean, standard deviation, and quartile range. The mean difference between all of the subjects' baseline attributes was compared using a student t-test. An independent t-test was used to compare the anthrometric and baseline in age and gender groups. The link between uric acid and HbA1c levels in both groups of patients was assessed using Pearson's correlation coefficient and multinomial logistic regression analysis for association. A p-value of <0.05 was judged statistically significant.

RESULTS

After receiving informed consent, 108 patients were enrolled in this research. 67 of the total 108 individuals had diabetes mellitus, and 41 had pre-diabetes. Participants in this study were found to be 59.12 years old on average, with a male preponderence.

Table 3: The mean age of participants

	N	Minimum	Maximum	Mean	Std. Deviation
Age in yrs	108	21	87	59.12	14.66

Table 4: Showing the gender distribution among study participants

		Frequency	Percent
Gender	Female	41	38.0
	Male	67	62.0
	Total	108	100.0

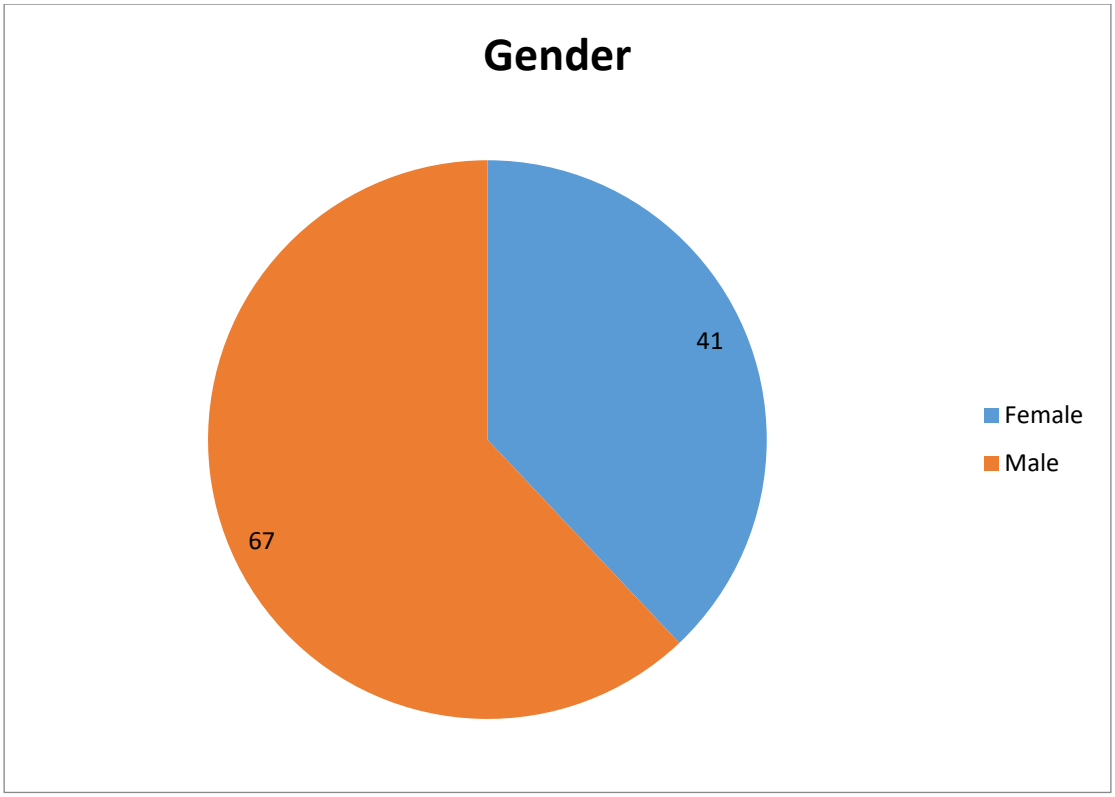

Figure 1: Showing the gender distribution among study participants

Table 5: Showing the mean level of height, weight and BMI of study participants

	N	Minimum	Maximum	Mean	Std. Deviation
Height in cm	108	145	175	161.12	6.674
Weight in kg	108	50	102	71.44	9.189
BMI kg/m^2	108	22.40	42.00	27.52	3.93

Table 6: Showing mean level of serum uric acid among study participants

	N	Minimum	Maximum	Mean	SD
Serum Uric acid in mg/dl	108	1.7	10.8	6.173	1.98

Table 7: Distribution of diabetes and pre-diabetes patients in present study			
		Frequency	Percent
HbA1c Group	Diabetes Mellitus	67	62.0
	Pre-diabetes Mellitus	41	38.0
	Total	108	100.0

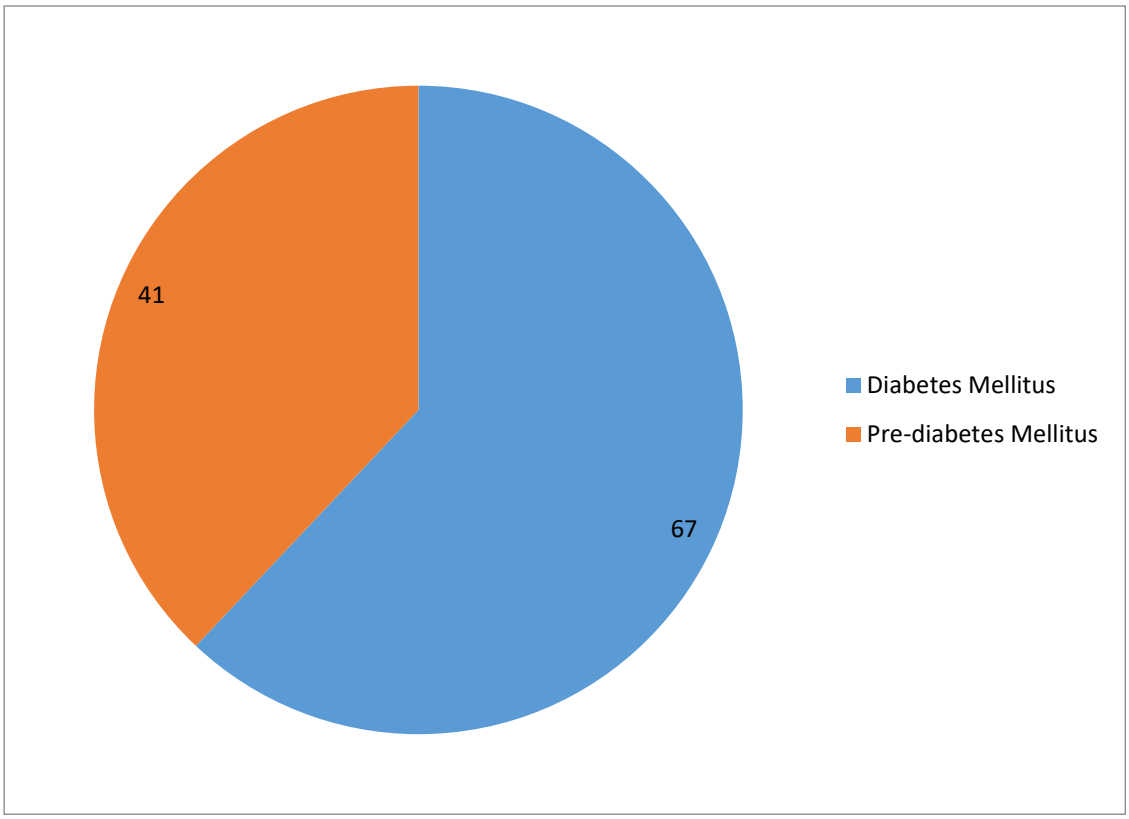

Figure 5: Distribution of diabetes and pre-diabetes patients in present study

Table 8: Showing the distribution of participants with habits			
		Frequency	Percent
Habits	None	71	65.7
	Smoker	23	21.3
	Tobacco chewing	14	13.0
	Total	108	100.0

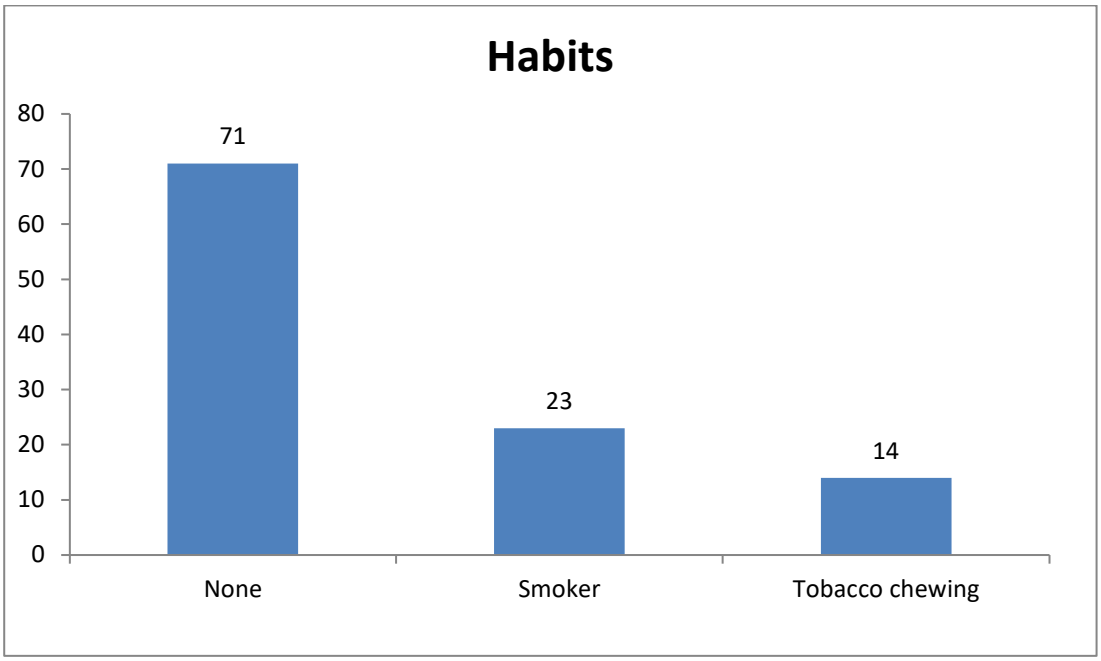

Figure 6: Showing the distribution of participants with habits

Table 9: Comparison of different habits between the groups				
		Diabetes Mellitus	Pre-diabetes Mellitus	Chi-square
		Count	Count	(p-value)
Habits	None	41	30	1.633 (0.442)
	Smoker	16	7	
	Tobacco chewing	10	4	

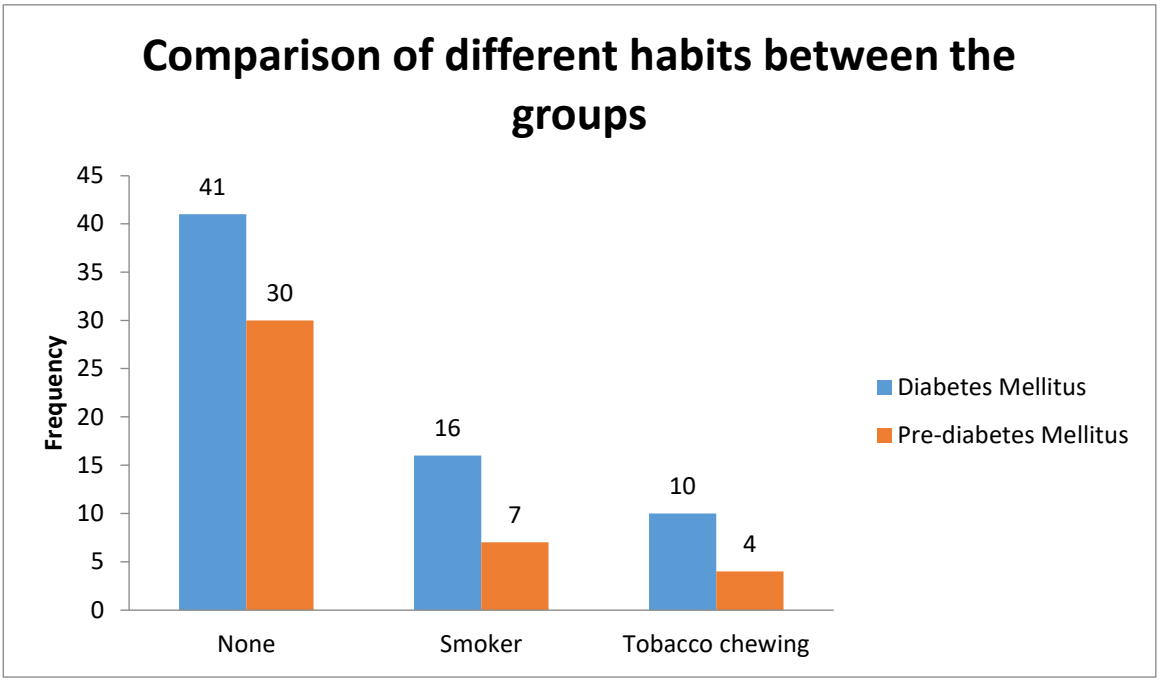

Figure 7: Comparison of different habits between the groups

Table 10: Mean of continuous variables compared between the two groups

	Diabetes Mellitus		Pre-diabetes Mellitus		Student t-test	
	Mean	SD	Mean	SD	t-value (df = 106)	Sig
Age in yrs	60.27	13.99	57.24	14.15	1.085	0.28
Height in cms	161.55	4.30	160.41	3.30	1.451	0.150
Weight in kg	76.79	9.34	73.22	5.21	2.241	0.02*
BMI in kg/m^2	29.43	3.80	28.38	2.31	1.593	0.114
HBA1C in %	9.2	2.3	6.0	.2	8.841	0.001**
Sr Uric Acid in mg/dl	6.76	3.1	5.5	1.9	1.900	0.03*

*p<0.05 is considered statistically significant; **p<0.001 is considered statistically highly significant.

Table 11: Showing the mean difference between the groups with BMI					
	Diabetes Mellitus		Pre-diabetes Mellitus		t-test (df=106)
	Mean	SD	Mean	SD	(p-value)
BMI	29.43	3.80	28.38	2.31	1.593 (0.114)

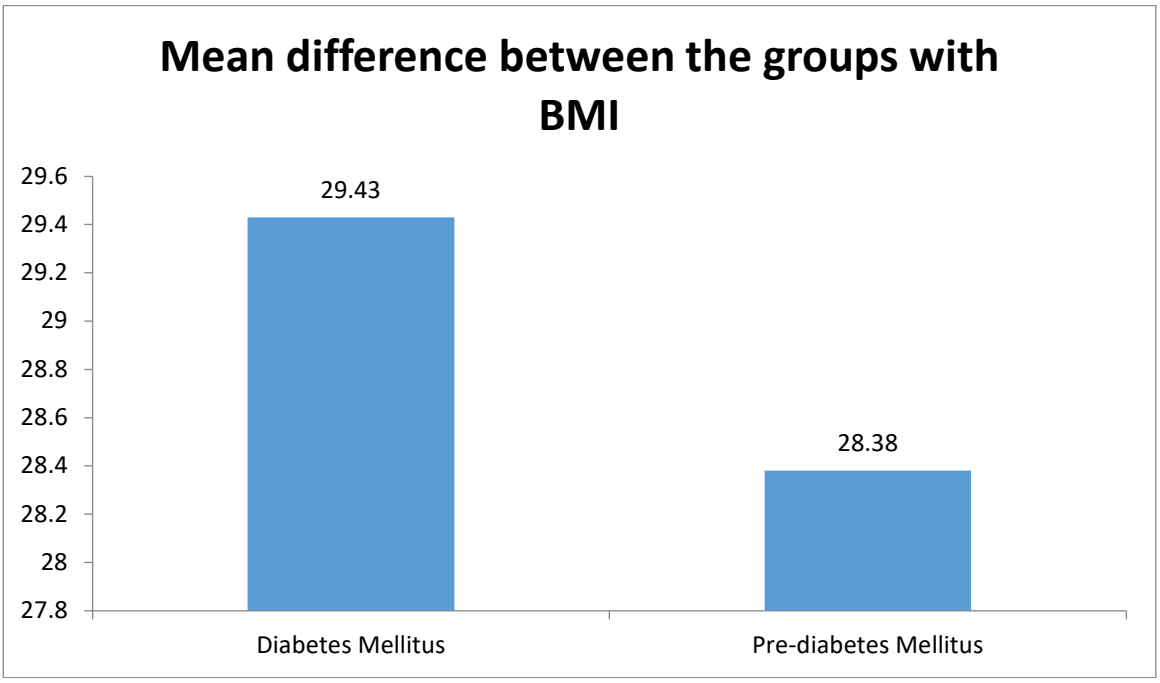

Figure 8: Mean difference between the groups with BMI

Table 12: Showing the presence of diabetic retinopathy			
		Frequency	Percent
Diabetic Retinopathy	NO	59	54.6
	YES	49	45.4
	Total	108	100.0

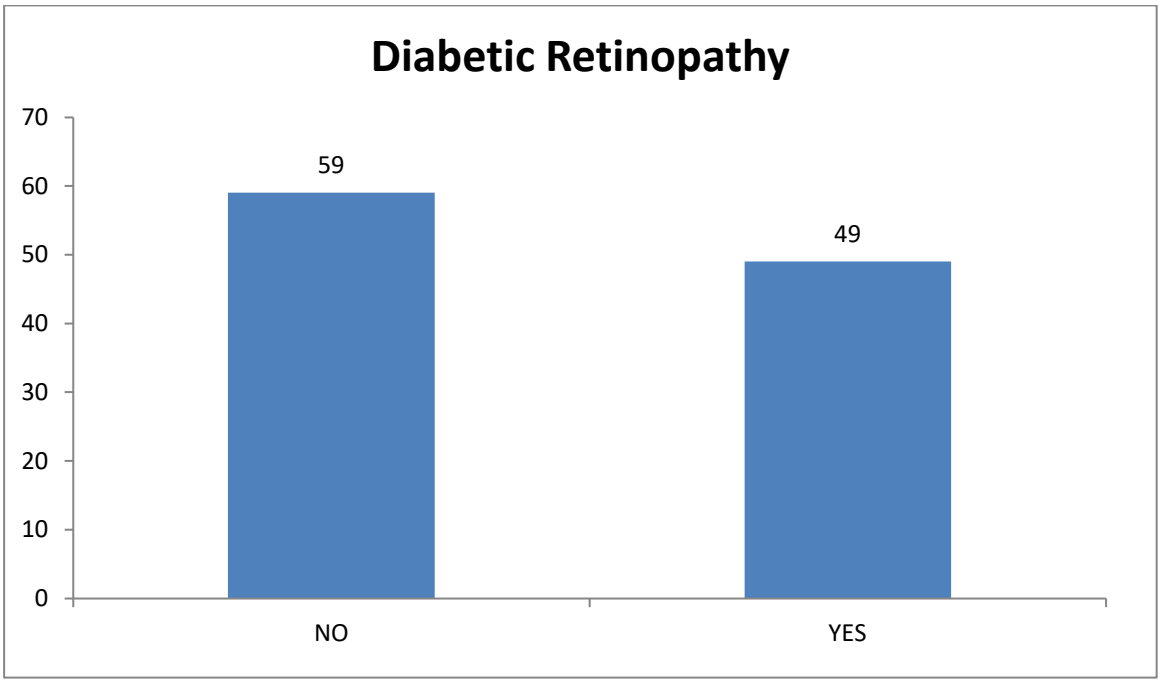

Figure 9: Showing the presence of diabetic retinopathy

Table 11: Showing comparison between the groups with diabetic retinopathy						
		Diabetes Mellitus		Pre-diabetes Mellitus		Chi-square
		Count	Column N %	Count	Column N %	(p-value)
Diabetic retinopathy	NO	18	26.9%	41	100.0%	54.88 (0.001)**
	YES	49	73.1%	0	0.0%	

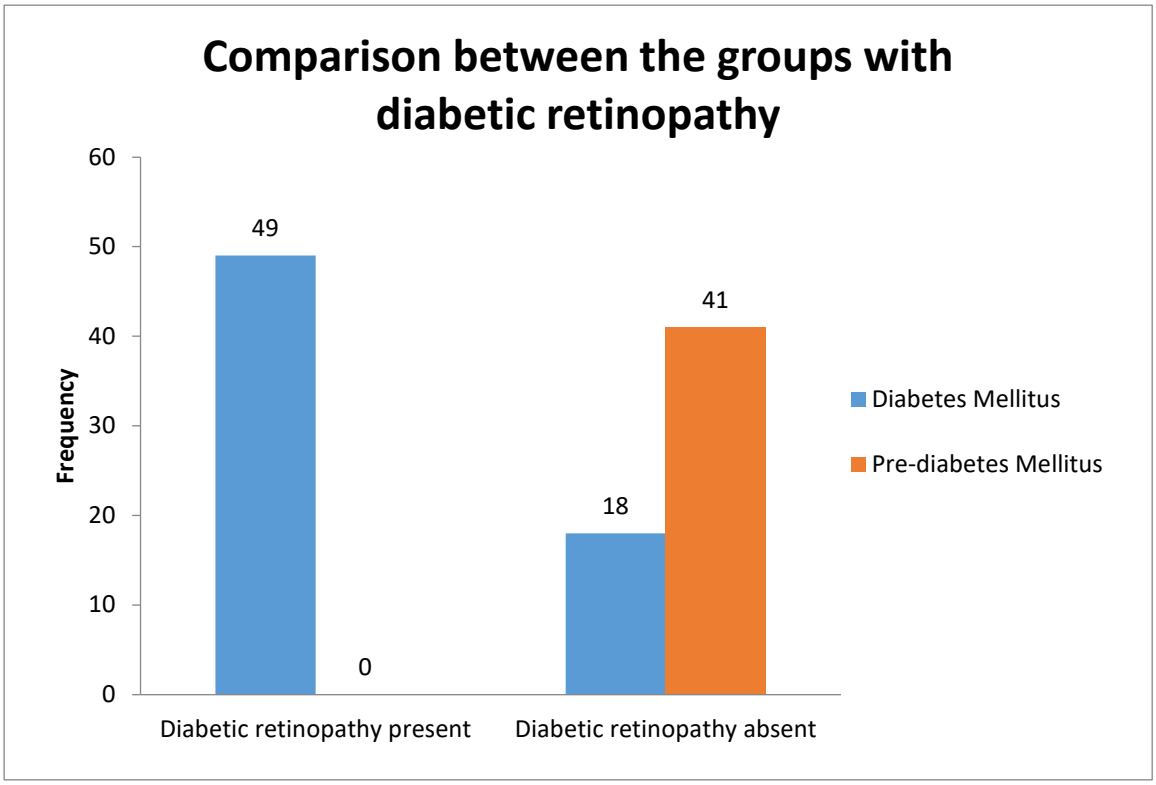

Figure 2: Comparison between the groups with diabetic retinopathy

Table 12: Comparison of mean difference between the two groups

	Diabetes Mellitus		Pre-diabetes Mellitus		Student t-test	
	Mean	SD	Mean	SD	t-value (df = 106)	Sig
HBA1C in %	9.2	2.3	6.0	.2	8.841	0.001**
Sr Uric Acid in mg/dl	6.76	3.1	5.5	1.9	1.900	0.03*

*p<0.05 is considered statistically significant; **p<0.001 is considered statistically highly significant.

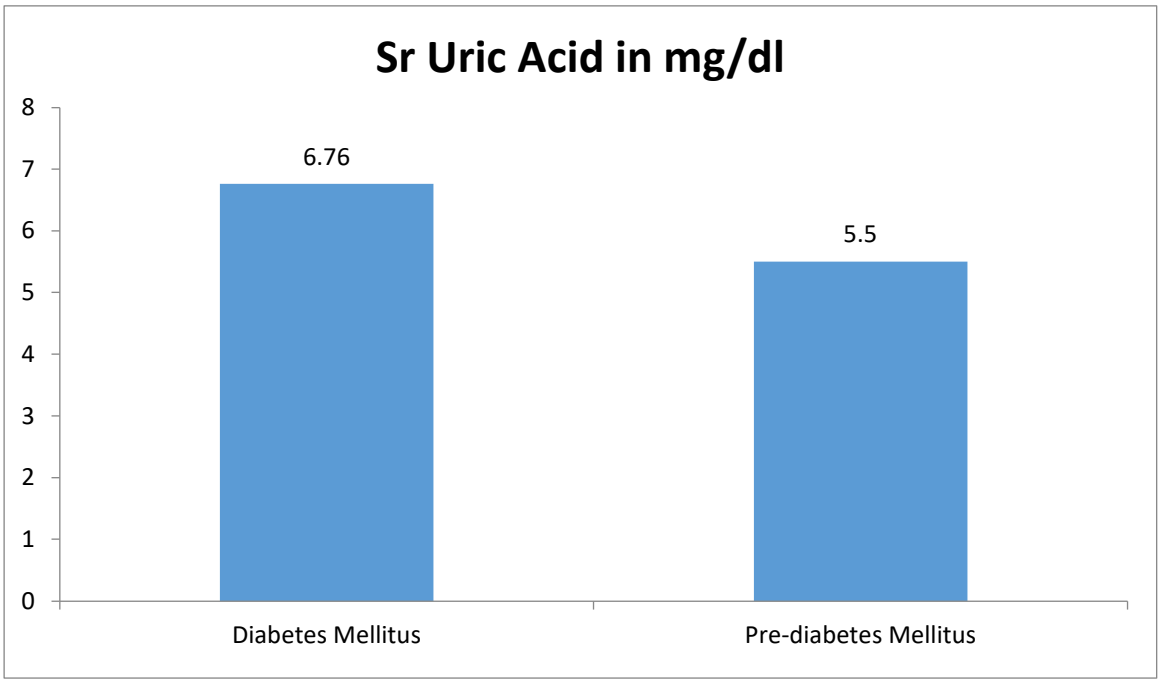

Figure 3: Comparison of uric acid mean difference between the two groups

Table 13: Showing Pearson's association between the HbA1c and uric acid.		
		Serum Uric acid
HBA1C in %	Pearson Correlation	.237*
	Sig. (2-tailed)	.014
*p<0.05 is considered statistically significant.		

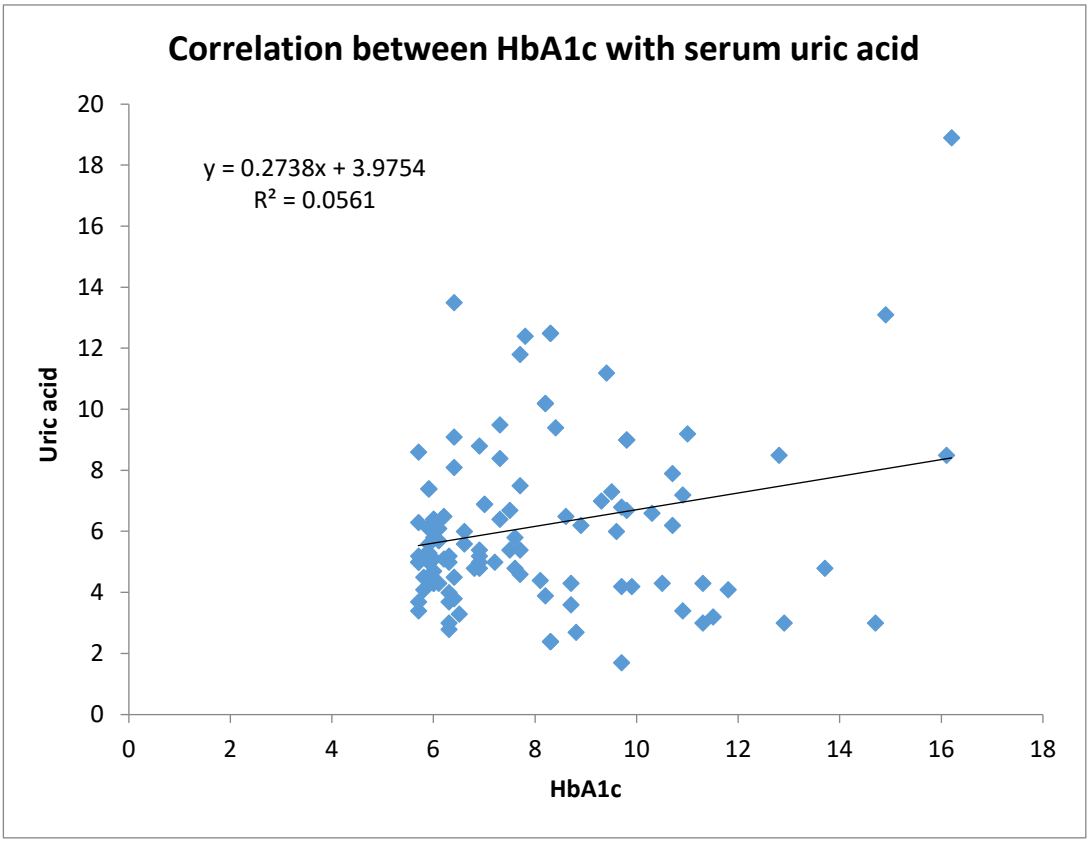

Figure 4: Showing Pearson's association between the HbA1c and uric acid.

DISCUSSION

HbA1c levels were correlated with uric acid levels in patients with prediabetes and type 2 diabetes mellitus in this observational investigation. An additional 41 patients had pre-diabetes in addition to the 67 patients who had diabetes. Twenty-three of the patients smoked cigarettes, while 23 of them smoked cigarettes.

The mean age of participants in present study was found to be 59.12±14.06yrs of age, with male predominance. At (57.24 ±14.15) years for those with prediabetes and (60.27± 13.99) years for those with diabetes, there was no statistically significant difference in age between the two groups. The mean weight among the patients with diabetes mellitus was significantly higher (76.79±9.34) than in the group of pre-diabetes (73.22±5.21). The mean height and BMI of the participants did not differ significantly between the two groups. In a study similar to this one, Haque T et al. found that men were more likely than women to have diabetes or pre-diabetes. (29)
The mean HbA1c was found to be (9.2±2.3) in patients with diabetes mellitus and (6.0±0.2) in participants with pre-diabetes. In this study, patients with diabetes were found to have a significantly higher incidence of diabetic retinopathy than those with pre-diabetes mellitus. However, there was no discernible difference between the two groups in terms of the distribution of habits.

The serum uric acid was substantially greater among the patients with diabetes mellitus (6.76±3.1mg/dL) compared to participants with pre-diabetes (5.5±1.9mg/dL). Rao et al., in a research similar to this one, found a greater mean of serum uric acid in those with diabetes and pre-diabetes mellitus. (33) Haque T et al. found that the serum uric acid level in diabetes mellitus patients was lower than in those with pre-diabetes, which is in contrast to the current study. (29)

There is a weak positive significant correlation between serum HbA1c with the serum uric Uric acid. Uric acid and blood glucose and HbA1c were found to be linked in studies by Dehghan A et al. and Chien K-L et al.(30,31). Studies done by Kramer CK et al. and Kodama S et al. identified a link between SUA and diabetes(37,38) however in a 16 year follow-up study of Japanese people, uric acid was found to be unrelated to a statistically significant increase in the risk of T2DM(39). A recent study by Modi AS and Sahi N in diabetic persons in India revealed no significant association between SUA and FBG.(40). Study on National Health And Nutrition Examination Survey Participants indicated that SUA levels were inversely associated with T2DM.(42)

CONCLUSION

There appears to be a poor association between HbA1c and serum uric acid among the people. A lower serum uric acid level was found in pre-diabetes mellitus than in diabetes mellitus. In persons with diabetes mellitus, there is an association between serum uric acid levels and HbA1c, but the correlation is modest.

LIMITATION OF THE STUDY

The limitation of this study is the smaller sample size. A larger sample size with long term follow up of the prediabetic population will help us in carrying out a detailed study to find out if serum uric acid can be used as a marker to measure oxidative stress and evaluate for microvascular and macrovascular complications in the Indian population.

SUMMARY

- Pre-diabetes and type 2 diabetes mellitus were included in this prospective, analytical observational study to see how uric acid and HbA1c correlate.
- Among the total 108 patients included, 67 were with diabetes mellitus and 41 had the pre-diabetes.
- The mean age of participants in this study was determined to be (59.12±14.06yrs) of age, with male preponderance.
- The mean age of the participants in Prediabetes mellitus was (57.24±14.15yrs) and (60.27±13.99yrs) among the diabetes mellitus, which was statistically not significant between the groups.
- The mean weight among the patients with diabetes mellitus was substantially greater (76.79±9.34) than in the group of pre-diabetes (73.22±5.21).
- The average height and BMI of the two groups were not significantly different.
- The mean HbA1c was found to be (9.2±2.3) in patients with diabetes mellitus and (6.0±0.2) in those with pre-diabetes.
- Among the patients, 14 were having habit of tobacco chewing and 23 had cigarette smoking and there was no significant difference between the two groups of participants in the distribution of the presence of smoking and chewing tobacco.
- Patients with diabetes mellitus had substantially greater levels of serum uric acid (6.763.1mg/dL) than those with pre-diabetes (5.51.9mg/dL).
- There is a slight positive significant connection between the serum HbA1c with the serum uric acid.
- The prevalence of diabetic retinopathy in patients with diabetes mellitus is greater than in people with pre-diabetes mellitus. ($p<0.05$).

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ANNEXURE I. ETHICAL CLEARANCE.

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to – be University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http://www.jnmc.edu
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Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 215 **Date: 24/12/2019**

To,
REG NO. BG0119012
PG student in Medicine,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"STUDY OF CORRELATION BETWEEN SERUM URIC ACID AND HbA1c IN PREDIABETIC AND DIABETICS – A ONE YEAR PROSPECTIVE ANALYTICAL STUDY "**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

32

ANNEXURE II

INFORMED CONSENT

Title Of Research Study: STUDY OF SERUM URIC ACID AND HBA1C CORRELATION IN PREDIABETICS AND DIABETICS- ONE YEAR HOSPITAL BASED PROSPECTIVE ANALYTICAL STUDY.

Principal Investigator:-
REG NO. BG0119012
Post Graduate Student,
Department Of General Medicine,
JNMC, Belagavi.

Guide:-
Dr. _____
Professor
Department of General Medicine,
JNMC, Belagavi.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your forearm for the investigations. It may cause swelling, pain, redness (rarely happens) at the site from where the blood is drawn.

You may not be benefitted by these investigations but you will be part of this study which is going to be useful to others in the future.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study. If you decide not to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

Does not apply to this research

Financial incentives for participation:

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results:

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

In case of the queries during study or in future you may contact following persons

REG NO. BG0119012 PROFESSOR DEPT OF GENERAL MEDICINE JNMC, BELAGAVI	**DR** _____ INVESTIGATOR PG IN GENERAL MEDICINE JNMC, BELAGAVI

CONSENT FORM

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me, this consent form and have had all the questions answered

Signature / Left Thumb print of the Participant or legally authorized representative

Participant's name

:……...

Signature / Left thumb impression of the participant :……...

Name of the legally authorized representative / guardian :……...

Signature / Left thumb impression :……...

Witness' name :……...

Signature / Left thumb impression :……...

Investigator's name and signature :……...

Date:

Place:

ANNEXURE III

PROFORMA

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

OCCUPATION

COMPLAINTS AT PRESENTATION:

Past history:

Family history:

Personal history:

Treatment history:

PHYSICAL EXAMINATION:

GENERAL CONDITION:

PALLOR- YES/NO
ICTERUS-YES/NO
LYMPHADENOPATHY-YES/NO
CYANOSIS- YES/NO
CLUBBING-YES/NO
EDEMA-YES/NO

VITALS:

PULSE:

RESPIRATORY RATE:

BLOOD PRESSURE:

HEIGHT:

WEIGHT:

BMI:

INVESTIGATION:

IP/OP NO	**HbA1C**	**SR.URIC ACID**	**DIABETIC RETINOPATHY**

SL.NO.	IP/OP NUMBER	AGE	SEX	HABITS	HEIGHT	WEIGHT	BMI	HBA1C	SR.URIC ACID	DIABETIC RETINOPATHY
1	1041066	65	F	none	159	58	22.9	9.7	1.7	YES
2	1042904	62	M	NONE	165	74	27.1	8.7	3.6	YES
3	1042873	25	M	SMOKER	163	66	24.8	8.3	2.4	YES
4	1043183	55	M	TOBACCO CHEWING	164	74	27.5	11.3	4.3	YES
5	1042851	65	F	NONE	159	78	30.8	8.2	10.2	YES
6	1042065	68	F	NONE	155	65	27	9.7	6.8	YES
7	1038028	55	M	TOBACCO CHEWING	169	75	26.2	16.2	18.9	YES
8	1036571	32	M	SMOKER	162	69	26.2	9.9	4.2	YES
9	1039491	65	M	NONE	172	82	27.7	10.5	4.3	YES
10	1016440	61	F	NONE	162	75	28.5	7	6.9	NO
11	1040172	61	M	SMOKER	170	80	27.6	10.9	3.4	YES
12	3699339	64	F	NONE	164	95	35.3	13.7	4.8	YES
13	1040929	60	M	TOBACCO CHEWING	169	64	22	7.7	4.6	NO
14	1021528	70	M	none	164	74	27.5	7.8	12.4	YES
15	1030274	65	F	NONE	164	84	31.2	10.3	6.6	YES
16	1034138	82	M	SMOKER	159	74	30.4	7.3	6.4	NO
17	1033459	80	M	NONE	164	70	26	8.9	6.2	YES
18	1033415	73	F	NONE	160	94	36.7	9.8	9	YES
19	1033268	72	M	SMOKER	168	88	31.2	11.3	3	YES
20	1034701	41	M	none	158	68	27.2	6.5	3.3	NO
21	1035217	65	M	none	165	79	29	8.3	12.5	YES
22	1035314	33	M	none	155	82	34	6.9	5.2	NO
23	1034790	70	M	none	155	62	25.8	8.4	9.4	YES
24	1015293	50	M	SMOKER	168	65	23	8.1	4.4	NO
25	1035364	74	M	SMOKER	163	75	28	11	9.2	YES
26	1036046	49	M	none	158	76	30	6.6	5.6	NO
27	5435043	48	M	none	162	75	28.5	8.8	2.7	YES
28	1015043	50	M	none	158	73	29.2	7	6.9	NO
29	1001689	65	F	none	162	92	35	11.8	4.1	YES
30	5571461	65	F	none	158	60	24	7.5	5.4	NO
31	757402	36	M	none	168	65	23	9.5	7.3	YES
32	2222142	40	M	SMOKER	155	102	42	12.9	3	YES
33	758994	71	M	SMOKER	163	68	25.5	7.6	4.8	NO
34	1021997	71	M	none	163	70	26.3	6.9	4.8	NO

35	1015959	35	F	none	158	69	27.6	6.4	9.1	NO
36	995856	72	M	SMOKER	156	72	29.5	5.8	4.5	NO
37	1037360	86	M	SMOKER	156	78	32	7.7	5.4	YES
38	1008470	63	F	none	158	70	28	6	4.3	NO
39	1080449	44	F	none	158	74	29.6	6	4.3	NO
40	1029186	62	F	none	156	82	33.6	5.9	7.4	NO
41	1032905	73	M	SMOKER	160	75	29.2	10.7	6.2	YES
42	1041768	47	M	SMOKER	160	78	30.4	5.7	3.7	NO
43	1020304	74	M	TOBACCO CHEWING	153	64	27.3	9.7	4.2	YES
44	1021036	63	M	none	163	78	29.3	8.2	3.9	YES
45	1031396	58	M	TOBACCO CHEWING	166	66	23.9	7.3	9.5	YES
46	1021621	75	F	none	162	86	32.7	9.8	6.7	YES
47	1022653	42	M	TOBACCO CHEWING	166	84	30	9.4	11.2	YES
48	1025506	21	M	none	156	84	34.5	5.7	5	NO
49	1027124	57	M	none	160	98	38.2	14.9	13.1	YES
50	1027520	66	F	none	165	74	27.1	7.5	6.7	NO
51	1028215	70	M	TOBACCO CHEWING	158	68	27.2	6.9	5	NO
52	1030653	63	M	TOBACCO CHEWING	155	78	32.4	9.3	7	YES
53	1032469	48	M	SMOKER	162	80	30.4	10.7	7.9	YES
54	1033416	73	F	none	163	82	30.8	9.8	9	YES
55	1035219	65	M	none	168	86	30.4	8.3	12.5	YES
56	1272063	87	M	SMOKER	164	86	31.9	9.6	6	YES
57	1036386	75	F	none	166	82	29.7	8.7	4.3	YES
58	1042635	76	M	TOBACCO CHEWING	154	72	28.4	6.2	6.5	NO
59	1042854	65	F	none	155	75	31.2	8.2	10.2	YES
60	1042878	25	M	SMOKER	155	69	28.7	8.3	2.4	YES
61	1042803	58	M	none	159	82	32.4	7.3	8.4	YES
62	747376	65	F	none	163	76	28.6	5.7	8.6	NO
63	1043501	57	M	none	162	69	26.2	6.4	3.8	NO
64	1045945	68	F	none	158	72	28.8	11.5	3.2	YES
65	1053062	45	F	none	164	78	29	7.7	7.5	YES
66	1027458	35	M	TOBACCO CHEWING	160	96	37.5	16.1	8.5	YES
67	1053054	55	F	none	158	83	33.2	12.8	8.5	YES
68	1029189	62	F	none	156	80	32.8	5.9	7.4	NO
69	1042527	48	M	none	158	72	28.8	6.4	13.5	NO
70	1043648	64	M	SMOKER	160	86	33.5	14.7	3	YES
71	1044206	76	F	none	165	80	29.3	6.9	8.8	YES

72	1044883	60	M	none	160	76	29.6	7.6	5.8	NO
73	1044762	72	F	none	162	68	25.9	6.3	2.8	NO
74	1046181	68	M	none	165	68	24.9	6.3	3.7	NO
75	1052248	40	M	SMOKER	163	75	25.2	5.7	3.4	NO
76	1053588	80	M	none	163	77	28.9	6.4	8.1	NO
77	5745099	56	F	none	162	69	26.2	6.4	4.5	NO
78	1042358	80	F	SMOKER	159	65	25.7	5.9	5.3	NO
79	1041799	81	M	SMOKER	159	76	30	6	6.4	NO
80	1043236	58	F	none	164	72	26.7	6.1	4.3	NO
81	1041900	55	F	none	162	78	29.7	6.3	4	NO
82	1042411	72	F	none	155	73	30	5.7	5.2	NO
83	1042239	58	F	none	166	75	27.2	6	5.1	NO
84	1036279	46	M	none	160	69	26.9	6.1	6.1	NO
85	1035230	58	M	none	159	65	25.7	5.9	6.1	NO
86	1035214	58	M	none	162	60	25.1	5.9	5.2	NO
87	1034865	65	F	none	166	70	25.6	6.3	3	NO
88	1031240	72	M	TOBACCO CHEWING	163	76	28.6	6	6.4	NO
89	5328779	42	F	none	160	77	30	6.3	5.2	NO
90	1372245	63	M	none	159	73	28.8	6	4.7	NO
91	954010	43	F	none	160	80	31.25	5.9	5.6	NO
92	5591039	60	M	TOBACCO CHEWING	156	66	27.1	5.8	4.1	NO
93	631748	78	M	SMOKER	159	75	29.8	6	5.8	NO
94	5715226	44	F	none	161	79	30.4	5.8	5.2	NO
95	1031022	58	M	TOBACCO CHEWING	163	72	27	5.9	5	NO
96	1021519	54	F	none	159	79	31.2	8.6	6.5	YES
97	1042962	35	F	none	165	76	27.9	6.1	5.7	NO
98	991075	35	M	SMOKER	168	82	29	5.7	6.3	NO
99	1012319	57	F	none	162	74	28.1	6.3	5	NO
100	5695468	49	M	none	165	72	28.2	7.2	5	NO
101	5757196	47	F	none	158	69	27.6	6.6	6	NO
102	1033104	60	M	TOBACCO CHEWING	157	68	27.5	6.8	4.8	NO
103	1045085	62	M	NONE	158	76	30.4	6	6.3	NO
104	1044574	50	M	SMOKER	159	85	33.6	10.9	7.2	YES
105	1044049	74	M	NONE	159	84	32.4	7.7	11.8	YES
106	1043555	70	M	NONE	163	75	28.2	6.9	5.4	NO
107	997818	44	F	NONE	159	72	28.4	6.2	5.1	NO
108	1043594	55	F	NONE	162	66	25.1	5.7	5	NO