"ASSOCIATION BETWEEN ELEVATED SERUM URIC ACID LEVELS AND ISLET BETA CELL FUNCTION INDICES IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS- A ONE YEAR CROSS SECTIONAL STUDY AT KLE'S DR PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTER"

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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
HOMA-IR	Homeostasis Model Assessment-Insulin Resistance
BMI	Body Mass Index
ADA	American Diabetes Association
MODY	Maturity Onset Diabetes of the Young
mmol/lmilimol per liter	
NAFLD	Non Alcoholic Fatty Liver Disease
PCOD	Poly Cystic Ovarian Disease
QUICKI	Quantitative Insulin Sensitivity Check Index
Log	Logarithm
FBS/FPG	Fasting Blood Sugar / Fasting Plasma Glucose
RIA	Radioimmunoassay
OGTT	Oral Glucose Tolerance Test
&And	
lbs Pounds	
h	Hour

A1C	HbA1c
NGSP	National Glycohemoglobin Standardization Program
DCCT	Diabetes Control and Complications Trial
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
mmeter	
cm	centimeter
WC	Waist Circumference
EGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiography
2D ECHO	2 Dimensional Echocardiography
RBC	Red Blood Cells
OHAs	Oral Hypoglycaemic Agents
pmol	Pico mole
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	PhosphoribosylDiphosphate
eg Example	
etcEt cetera	
TG	Triglyceride
NO	Nitric Oxide
eNOS	Endothelial Nitric Oxide Synthase
O_2^-	Superoxide
XO	Xanthine Oxide
$ONOO^-$	Peroxynitrite
dlDeciliter	
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
P-ERK	Pancreatic Extracellular signal Regulated Kinase
P-AMPK	Pancreatic Adenosine Monophosphate – activated Protein
Kinase	
Dept	Department
HbA1C	Glycosylated Haemoglobin
mlMililiter	
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

TITLE: - "ASSOCIATION BETWEEN ELEVATED SERUM URIC ACID LEVELS AND ISLET BETA CELL FUNCTION INDICES IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS- A ONE YEAR CROSS SECTIONAL STUDY AT KLE'S DR PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTER"

INTRODUCTION:-T2DMhas evolved into a silent epidemic as well as a substantial universal health burden. Keeping in mind its ubiquity, and multiple complications it give rise to, it is crucial to diagnose it as promptly as possible. SUAis unfolding as a possible marker of DM risk. Lately it's been hypothesised that high SUA may be a potential precursor for the development of DM rather than just a consequence of IR. Even though various animal and clinical studies concluded that SUA plays an essential role in the onset of DM, the association between SUA and pancreatic islet β cell function is still unclear.

AIMS AND OBJECTIVES:- To study the association between elevated serum uric acid levels and islet β cell function index in newly diagnosed type 2 diabetes mellitus.

MATERIALS AND METHODS:- A Hospital based one year Cross-sectional Study was conducted in the Department of Medicine, KLE'S Dr.Prabhakar Kore Hospital and Medical Research Centre, Belagavi from 1st January 2019 to 31st December 2019 and required data was collected from 76patient who were newly diagnosed T2DM.

All the patients were investigated for SUA, and HOMA-IR was calculated using the HOMA2 Calculator.

RESULTS: -In the present study there was a male preponderance (72.4% - male; 27.6 % - female), with male to female ratio of 2.62 : 1. Majority of the patients were > 60 years of age (32.89%), and the mean age was 53.76 ± 13.33 years. The prevalence of hypertension among the study population was 48.7 %. The most common habit was tobacco consumption (55.3%). 46.1 % of the patients had a family history of DM. Most of the patients were obese (75 %), with a mean BMI of 27.19 ± 3.23 kg/m^2. The mean SUA level among the male study population was 4.65 ± 1.81 mg/dl and among the females, it was 4.31 ± 1.94 mg/dl. The β pancreatic cell function index was estimated using HOMA-IR. The mean HOMA-IR level among the male study population was 5.01 ± 7.44 & 5.02 ± 4.63 among the female study population. A positive and significant correlation was observed between SUA & HOMA-IR (r=0.2283, p=0.0489) at 5% level, & the correlation was more pronounced among the female population (r=0.5127, p=0.0175). Correlation between HOMA-IR & BMI was found to be positive & significant (r=0.4948, p=0.0001). A negative correlation was noted between SUA & HbA1C (r = -0.0015, p = 0.9948). On plotting multiple regression analysis, coefficient of determination (R^2) was 0.8374 ($p<0.05$), indicating significant contribution of all variables when combined towards HOMA-IR.

CONCLUSION:- The present study demonstrated that serum uric acid harbours a positive and significant correlation with pancreatic islet β cell function index (calculated using HOMA-IR) among patients of type 2 diabetes mellitus who are newly diagnosed and is influenced by gender andBMI.

KEYWORDS:-

Newly diagnosed T2DM, Serum Uric Acid, pancreatic islet β cell function, HOMA-IR

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INTRODUCTION

T2DM, a chronic metabolic disorder, with its dramatically rising prevalence over the past 2-3 decades, has evolved into a silent epidemic as well as a substantial universal health burden. India occupies the top 5 ranking in the prevalence of DM, with approximately 77 million population living with DM as of 2019 according to the latest survey done by IDF. [1]

Even with better comprehension of its pathophysiology, recognising which of the patients are at utmost risk of developing critical complications related to DM is an unceasing challenge.[2]

Therefore, keeping in mind the ubiquity of T2DM, and the multiple micro as well as macrovascular complications it gives rise to, it is crucial to diagnose it as promptly as possible to maintain accurate glycemic control and defer the development of complications.[3]

The pathology of DM can range from severe IR with relative insulin deficiency to severe insulin deficiency with IR. The initial stage of diabetes is characterized by the stage of compensation i.e. increased insulin secretion in order to keep up normoglycemia when there is IR along with reducing mass of the β-cells.[4,5]

Based on this, SUA is unfolding as a possible marker of DM risk. UA, which is a breakdown product of metabolism of purine, is majorly excreted from the body via kidneys, where the glomeruli filters it and the proximal tubules excretes it. [6,7]

The levels of SUA in a person is a blended result of genetics as well as multiple life style factors including eating habits, exercise, type of work etc. Hence Indian population by virtue of different food practices, lifestyle along with genetic constitutions compared to other populations in the world, will have varying levels of SUA. [8]

Past studies have revealed that SUA is a risk factor for multiple chronic diseases, including cardiovascular disorders, HTN, as well as kidney diseases. [9,10]

Lately it's been hypothesised that high SUA may be a potential precursor for the development of DM rather than just a consequence of IR, i.e. a causal role of SUA. [11,12]

Even though various animal as well as clinical studies concluded that SUA plays an essential role in the onset of DM by virtue of inflammatory processes along with oxidative stresses, the association between SUA and pancreatic islet β cell function is still unclear. [13]

Thus this hospital based cross sectional study aims to associate SUA levels to pancreatic islet function index (by calculating IR using HOMA-IR) in cases of newly diagnosed T2DM as well as to examine whether SUA levels in T2DM are affected by gender, age & BMI.

OBJECTIVES

The objective is to study the association between elevated serum uric acid levels and pancreatic islet β cell function index in newly diagnosed type 2 diabetes mellitus.

REVIEW OF LITERATURE

HISTORICAL NOTE

Term "Diabetes", first used by Roman Physician Aretaeus (2nd century A.D.), implies "to pass through". Charaka and Sushruta in four hundred to five hundred B.C. had described as well as classified DM in their texts. But the 1st report of diabetes was found on an Egyptian Papyrus dated 1552 B.C.[14]

In 1869, German Medical Student Paul Langerhans, discovered two types of cells in pancreas, one secreting normal pancreatic juices and the other, whose function was unknown, were recognized to be the "islets of Langerhans" years later. [15] In the year 1901, E.L. Opie ascertained that destruction of these islets results in DM. [16]

In 1921, an orthopedician, F.G. Banting, and a medical student, Charles. H. Best, removed pancreas of dogs, isolated fluid from the islets of Langerhans and tried to see if glycosuria could be suppressed using this fluid. Later this pancreatic fluid was named Isletin and was extracted by Professor of Physiology, James Macleod and Biochemist J.B. Collip. For this Banting and MacLeod were presented Nobel Prize for Medicine in 1923 which they shared with Best and Collip. [17]

DEFINITION –

In 1997, the American Diabetes Association (ADA) defined diabetes as "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both."[18]

Diabetes is a serious, chronic disease with significant morbidity and mortality worldwide.

EPIDEMIOLOGY

According to ADA, the approximate prevalence of DM, which was 7.4% in 1995, is predicted to increase to ~9% in 2025. [19] According to IDF (International Diabetes Federation) Diabetes Atlas (9th edition), 463 million people worldwide live with diabetes, and a predicted 578 million people by 2030 and 700 million by 2045 will be suffering from this disease. [20]

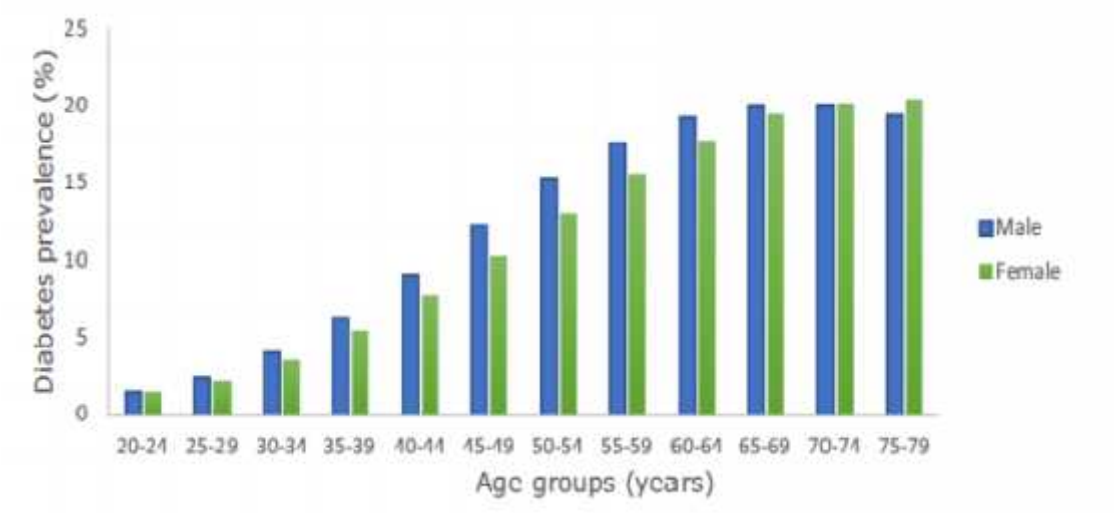


Figure 1 - Diabetes prevalence by age and sex in 2019.

RANK	COUNTRY	NUMBER OF PEOPLE WITH DIABETES IN MILLION
1	CHINA	116.4
2	INDIA	77.0
3	USA	31.0
4	PAKISTAN	19.4
5	BRAZIL	16.8

Table 1 - Top 5 countries with diabetes (20–79 years) in 2019

The prevalence of DM is increasing more expeditiously in low/middle-income countries compared to the higher ones.

CLASSIFICATION OF DIABETES MELLITUS[21] :

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types
   A. Genetic defects of β-cell function
      1. MODY 3 (Chromosome 12, HNF-1α)
      2. MODY 1 (Chromosome 20, HNF-4α)
      3. MODY 2 (Chromosome 7, glucokinase)
      4. Other very rare forms of MODY (e.g., MODY 4: Chromosome 13, insulin promoter factor-1; MODY 6: Chromosome 2, *NeuroD1*; MODY 7: Chromosome 9, carboxyl ester lipase)
      5. Transient neonatal diabetes (most commonly ZAC/HYAMI imprinting defect on 6q24)
      6. Permanent neonatal diabetes (most commonly KCNJ11 gene encoding Kir6.2 subunit of β-cell K_{ATP} channel)
      7. Mitochondrial DNA
      8. Others
   B. Genetic defects in insulin action
      1. Type A insulin resistance
      2. Leprechaunism
      3. Rabson-Mendenhall syndrome
      4. Lipoatrophic diabetes
      5. Others
   C. Diseases of the exocrine pancreas
      1. Pancreatitis
      2. Trauma/pancreatectomy
      3. Neoplasia
      4. Cystic fibrosis
      5. Hemochromatosis
      6. Fibrocalculous pancreatopathy
      7. Others
   D. Endocrinopathies
      1. Acromegaly
      2. Cushing's syndrome
      3. Glucagonoma
      4. Pheochromocytoma
      5. Hyperthyroidism
      6. Somatostatinoma
      7. Aldosteronoma
      8. Others
   E. Drug or chemical induced
      1. Vacor
      2. Pentamidine
      3. Nicotinic acid
      4. Glucocorticoids
      5. Thyroid hormone
      6. Diazoxide
      7. β-Adrenergic agonists
      8. Thiazides
      9. Dilantin
      10. γ-Interferon
      11. Others

F. Infections
   1. Congenital rubella
   2. Cytomegalovirus
   3. Others

G. Uncommon forms of immune-mediated diabetes
   1. Stiff-man syndrome
   2. Anti-insulin receptor antibodies
   3. Others

H. Other genetic syndromes sometimes associated with diabetes
   1. Down syndrome
   2. Klinefelter syndrome
   3. Turner syndrome
   4. Wolfram syndrome
   5. Friedreich ataxia
   6. Huntington chorea
   7. Laurence-Moon-Biedl syndrome
   8. Myotonic dystrophy
   9. Porphyria
   10. Prader-Willi syndrome
   11. Others

IV. Gestational diabetes mellitus

Table 2 – Etiological classification of DM

TYPE 2 DIABETES MELLITUS –

It's the most common form of diabetes worldwide, making up for approximately 90% of the total diabetes load. According to the current understanding of pathogenesis of T2DM, it is caused by a complex interplay between two main factors – "Insulin Resistance (IR)" and "Insulin secretory defect (Insulin deficiency)". Thus the pathology of T2DM can range from severe IR accompanied by relative insufficiency of insulin to extreme insulin deficitand IR. [22]

Its progression can be regarded to have five stages which are characterized by alterations in numerous metabolic parameters as well as β-cell function.

- Stage I = Compensation

  It is a phase of increased insulin secretion in order to keep up normoglycemia,when there is IR along with reducing mass of the β-cells.

- Stage II = Stable adaptation

As the levels of glucose begin to increase, reaching approximately 5.0 mmol/l (90mg/dl) – 6.5 mmol/l (117mg/dl), there occurs a steady state of adaptation of β-cell along with β-cell mass loss as well as disarrayed function.

- Stage III = Unsteady early decompensation

It is a transient unstable phase of early decompensation where glucose levels increase swiftly to frank diabetes.

- Stage IV = Stable decompensation

It is associated with more profound β-cell dedifferentiation.

- Stage V = Severe decompensation

It represents a stage of drastically reduced β-cell mass associated with advancement to ketosis. [23]

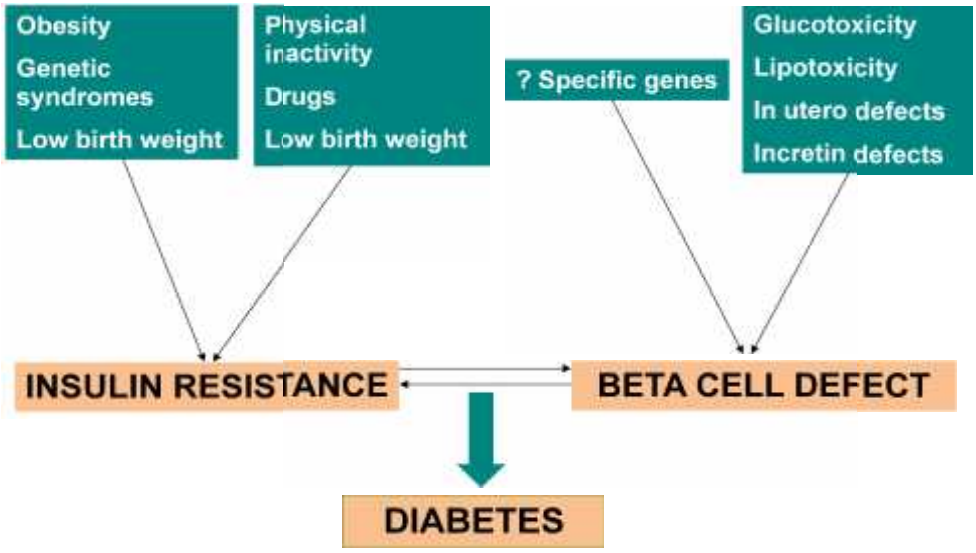


Figure 2 – Pathogenesis of T2DM

Insulin resistance

IR is defined as subnormal response produced by a normal amount of insulin. It can be congenital or acquired. The most important cause being obesity, especially abdominal obesity. [24]

It is an independent risk factor for T2DM, metabolic syndrome, cardiovascular disease as well as total cancer mortality.

Resistance to insulin action can occur at the level of insulin receptor or at the post receptor pathways. [25]

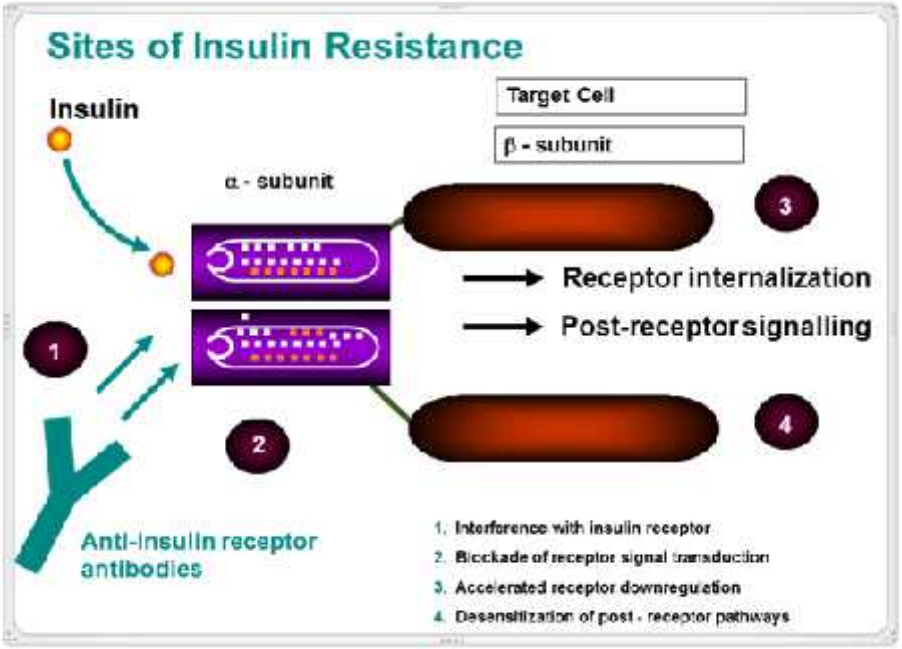


Figure 3 - Sites of IR

Major sites of IR include liver, skeletal muscle and adipose tissue.

First Phase - Normal plasma glucose due to compensatory increase in insulin secretion.

Second Phase- Worsening of IR leading to post-prandial hyperglycemia despite elevated insulin secretion.

Third Phase - IR remains constant; there is decline in β cell function producing fasting hyperglycemia. [26]

Common clinical correlates of IR include–

- Obesity
- NAFLD
- Diabetes or dysglycemia
- PCOD
- Skin changes (Acanthosisnigricans, skin tags) [27,28]

Measurement of IR-

- Gold standard -**Hyperinsulinemiceuglycemic clamp**

  (difficult to perform and time consuming)

- Simpler calculated indices -
  - Homeostasis Model Assessment-Insulin Resistance (HOMA-IR)
  - Quantitative Insulin Sensitivity Check Index (QUICKI)
  - Matsuda Index
- Biochemical markers example- Insulin- like growth factor-binding protein-1

QUICKI = $1/(\log I_0 + \log G_0)$

I_0 – fasting plasma insulin concentration

G_0 - fasting plasma glucose concentration

QUICKI is log HOMA-IR, hence has a near perfect correlation

$$ISI_{(MATSUDA)} = 1000 / \sqrt{G_0\ I_0\ G_{MEAN}\ I_{MEAN}}$$

Matsuda Index =

I_0 – Fasting plasma insulin concentration (mIU/l),

G_0 – Fasting plasma glucose concentration (mg/dl),

G_{mean} – Mean plasma glucose concentration during OGTT (mg/dl),

I_{mean} – Mean plasma insulin concentration during OGTT (mU/l),

10,000– Simplifying constant to get numbers from 0 to 12.

√– Correction of the nonlinear values distribution.

HOMA –

- HOMA, which is a paradigm model for assessment of pancreatic islet β cell function as well as IR from FBS & concentrations of either serum insulin or serum C-peptide , was first developed by Matthews *et al*. in 1985.
- The relation among glucose and insulin in the basal state mirrors the harmony between hepatic glucose yield and secretion of insulin, which is kept up by a feedback circle among the liver and β cells of pancreas. [29]
- **HOMA1**: (original HOMA model)

$$\text{HOMA1-IR} = (\text{FPI} \times \text{FPG})/22.5$$
$$\text{HOMA1-\%B} = (20 \times \text{FPI})/(\text{FPG} - 3.5)$$

(for IR and β cell function, respectively)

FPI = fasting plasma insulin concentration

FPG = fasting plasma glucose

- **HOMA2**: (updated HOMA model)

It is a computer based model that also considers variations in hepatic as well as peripheral resistance of glucose.

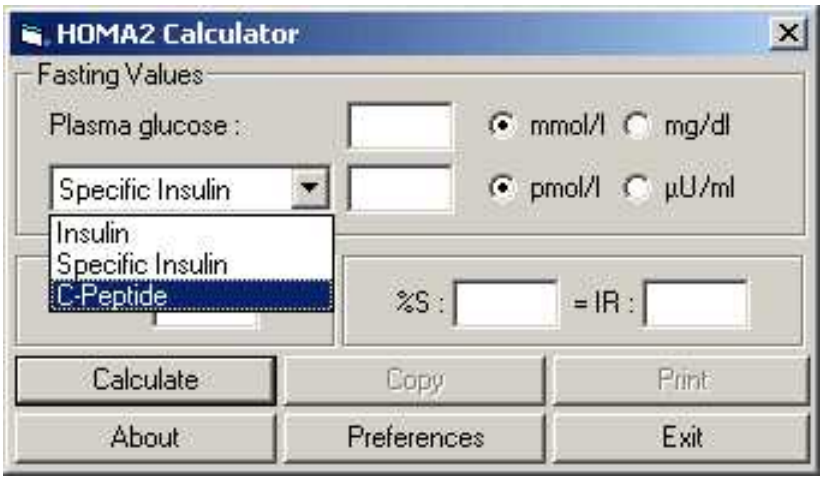


Figure 4 –HOMA2 Calculator

HOMA2 model can be used to calculate –

1. insulin sensitivity (%S)
2. β cell function (%B) and
3. IRfrom FBS and one of the following
    - RIA insulin
    - specific insulin
    - C-peptide.

- Since secretion of insulin is pulsatile, theoretically to calculate HOMA, it is superior to take mean of 3 samples at a gap of five minutes rather than only one sample; but practically a single sample is used , which reproduces similar results in large datasets. [30]
- Various studies have compared the efficacy of HOMA with other well validated methods used for calculating IR and β cell function and have

identified a satisfactory strong correlation among IR values obtained from HOMA &normoglycemic clamp (R_s = 0.88, P < 0.0001; R_s=0.85, P<0.0001*)* as well as that ofβ cell function calculated using HOMA &hyperglycaemic clamps (R_s= 0.61, P < 0.01) .

- The standard reference values for HOMA-IR and HOMA-B vary on the basis of ethnicity as well as sex.
- According to some studies, values of HOMA-IR

  > 1.9 signifies early IR.

  > 2.9 signifies notable IR

  Some Indian studies have mentioned a value of <2.5 as normal [31]

SCREENING OF T2DM

The aim of screening is to recognise asymptomatic people expected to have DM.It is needed in T2DM as -

Majority of diabetics are asymptomatic and unaware of the presence of the disorder initially.

1) Epidemiologic data imply that T2DM may exist in an individual for up to a decade before it is diagnosed.
2) People may have ≥1 complications of T2DM at diagnosis.
3) Once treatment of T2DM is initiated, there may be a favourable conversion of the natural history of DM.

FPG & 75-g OGTT are both acceptable as screening investigations. FPG is favoured in clinical settings considering it is simpler, swift to carry out, more agreeable with the patients and more economical. [32]

Recommendations
Evaluation for type 2 diabetes should be performed within the health care setting. Patients should be screened at 3-year intervals beginning at age 45; testing should be considered at an earlier age or be carried out more frequently if diabetes risk factors are present.
Diabetes risk factors include a family history of diabetes; overweight defined as BMI ≥25 kg/m^2; habitual physical inactivity; belonging to a high-risk ethnic or racial group; previously identified IFG or IGT; hypertension; dyslipidemia; history of GDM or delivery of a baby weighing >9 lbs; and polycystic ovary syndrome.
The FPG is the recommended screening test. The OGTT may be necessary for the diagnosis of diabetes when the FPG is normal. The FPG is preferred for screenings because it is faster and easier to perform, more convenient, acceptable to patients, and less expensive.
Diagnostic testing should be performed in any clinical situation in which such testing is warranted; health care providers should not consider whether a person meets screening criteria in such cases.
Screening outside of health care settings, or community screening, has not been shown to be beneficial and may result in some harm; this type of screening is not recommended.

Table 3 - Major recommendations for screening of T2DM

DIAGNOSIS OF DM

According to ADA 2020, criteria for diagnosis of DM is as follows –

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Table 4 - Diagnosis of Diabetes Mellitus (ADA 2020)

As mentioned in the table, diagnosis of DM needs 2 elevated values from any 2 samples -either same samples or separate samples (performed without delay).

In case of conditions which can directly or indirectly impact haemoglobin glycation, instead of HbA1C, only Plasma Glucose should be used for diagnosis of DM. These conditions include the following –

- sickle cell disease,
- pregnancy (2^{nd}, 3^{rd} trimesters and post partum),
- G6PD deficiency,
- HIV,
- hemodialysis,
- recent blood loss or transfusion,
- recent erythropoietin therapy. [33]

PREDIABETES (Impaired glucose homeostasis)

It is the term used for people with sugar values not satisfying the criteria for DM but too elevated to be regarded as normoglycemic. It is associated with increased risk for DM as well as cardiovascular diseases.

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

Table 5- Criteria defining Prediabetes (ADA 2020)

Impaired Fasting Glucose (IFG) –

According to ADA, IFG is considered as Fasting Plasma Glucose (FPG) ≥ 100 mg/dl and ≤125 mg/dl, whereas according to WHO, IFG is FPG ≥ 110 mg/dl and ≤125 mg/dl.

Impaired Glucose Tolerance (IGT) –

According to both ADA and WHO, IGT is 2 hour Plasma Glucose during 75-g oral glucose tolerance test (OGTT) ≥140 mg/dl and ≤ 199 mg/dl. [34]

Patients who fit in the criteria for pre diabetes should be tested yearly for diabetes.

Following are the individuals who are at high risk for developing pre diabetes or DM –

1. Family history of DM
2. Overweight
3. Habitual physical inactivity
4. Race/ethnicity (e.g., African-Americans, Hispanic-Americans, Native Americans, Asian-Americans)
5. Previously identified IFG or IGT
6. Hypertension
7. HDL cholesterol ≤ 35 mg/dl and/or TG ≥ 250mg/dl
8. History of GDM or delivery of a baby weighing > 9 lbs
9. PCOD [35]

Thus natural history of DM can be summarised as shown in the following figure -

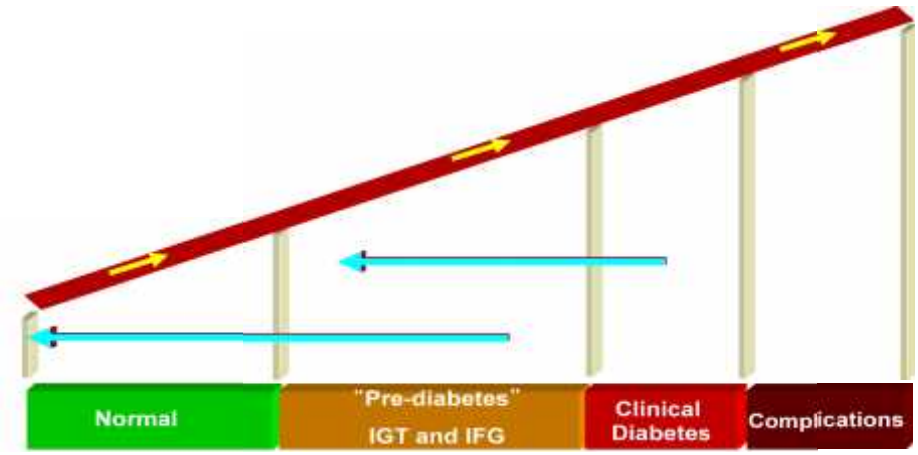


Figure 5 – Natural history of Diabetes[36]

Once the diagnosis of T2DM is made, following work up should ideally be carried out in the patients –

1) PHYSICAL EXAMINATION –
    - Anthropometry – BMI, waist circumference etc.
    - Vitals – Pulse (including peripheral pulses), BP
    - Insulin resistance (IR) markers – skin tags, acanthosisnigricans
    - Foot examination
    - Fundoscopy[37]

<u>BMI</u> –

$$BMI = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

For Asian population, BMI is categorized as follows – [38]

Underweight	<18.5kg/m^2
Normal	8.5-22.9 kg/m^2
Overweight	23.0-24.9 kg/m^2
Obese	≥25 kg/m^2

Table 6 – Classification of BMI

Waistcircumference –

- It correlates well with subcutaneous as well as intra-abdomoinal fat mass.
- Considered as increased risk of cardiometabolic diseases if WC > 102 cm (male) or 88cm (female). [39]

Foot examination –

- Inspection for any ulcers, deformities, callus etc
- Palpation of peripheral pulses (dorsalispedis, posterior tibial artery)
- Ankle Jerk
- Ankle Brachial Index
- Posterior column sensations – proprioception and vibration
- Monofilament test [40]

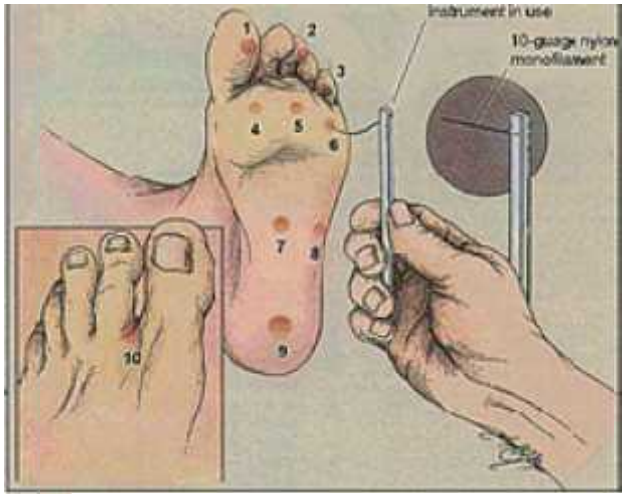


Figure 6 – Monofilament Test

Fundoscopy –

To recognize diabetic retinopathy, which is the most common microvascular diabetic complication.[41]

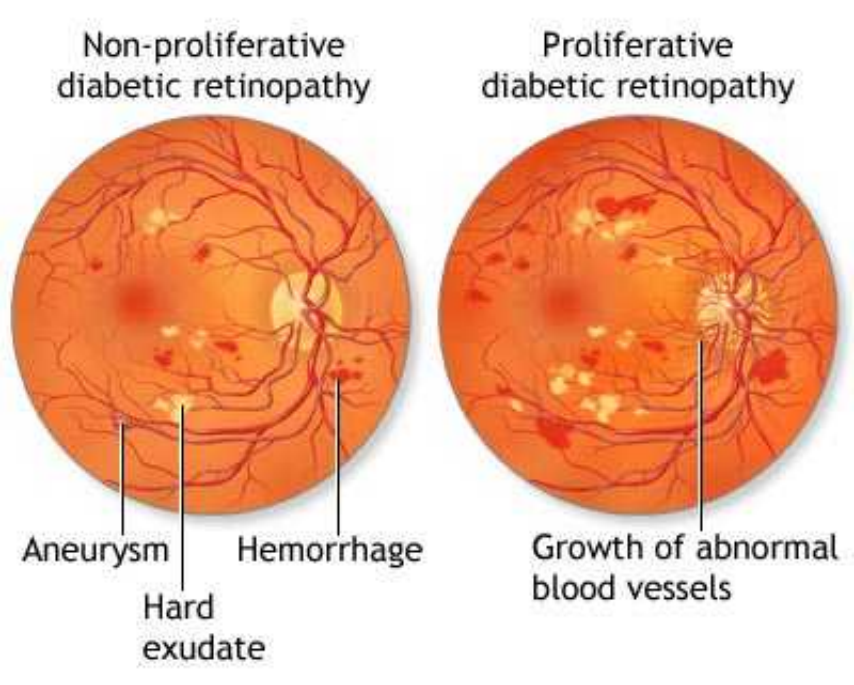


Figure 7 - Fundoscopic changes in DM

2) INVESTIGATIONS -

The basis of investigations in T2DM is –

i. Confirmation

ii. To evaluate for severity of DM & treatment response

iii. Complications – acute as well as chronic

After confirmation of T2DM, in a newly diagnosed case, following investigations should be done routinely –

i. HbA1c (if not already done before for confirmation of DM)

ii. Fasting lipid profile

iii. Liver and kidney function tests along with EGFR

iv. Urine test – for assessing microalbuminuria

v. ECG, 2D ECHO (when required)

vi. TSH

vii. C – Peptide (in selected cases) [42]

HbA1c -

It indicates mean blood sugars during the extent of RBC lifespan i.e., approximately 120 days.

Test results do not alter with

- Timing
- Meals
- Drugs – insulin or OHAs
- Acute stress
- Exercise [43]

Target HbA1c, once the diagnosis of DM is confirmed, is <7 % (according to ADA).

BLOOD GLUCOSE		STATUS	HbA1c	
mmol/L	mg/dL		%	mmol/mol
5.4	97	Normal	5	31
7.0	126		6	42
8.6	155	Pre-Diabetes	7	53
10.2	184	Diabetes	8	64
11.8	212	Diabetes	9	75
13.4	241		10	86
14.9	268	Diabetes	11	97
16.5	297		12	108

Table 7 – HbA1c and DM control

Microalbuminuria–

Defined as urine albumin 30-300mg/24 hour urine.

Its presence is a powerful prognosticator of development of cardiovascular as well as renal complications in DM. [44]

C-Peptide– (normal levels – 0.3 – 0.6 pmol/ml)

It's a polypeptide byproduct of insulin synthesis.

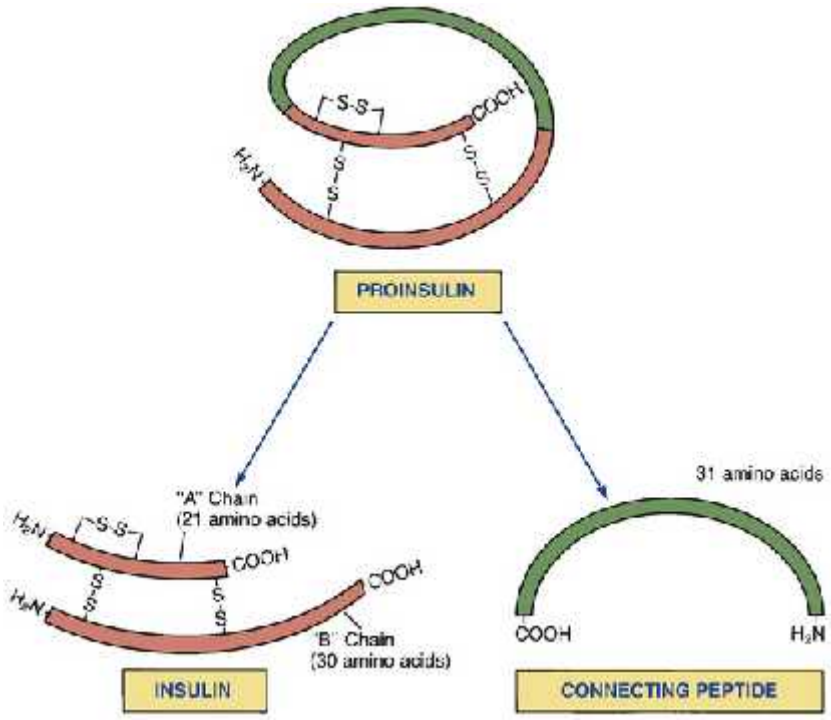


Figure 8 – Formation of C-peptide from Proinsulin

Significance in DM –

- To differentiate T2DM from T1DM and LADA
- To assess pancreatic β cell function (eg to calculate HOMA-IR)
- To help decide therapy and their response.

Since it is metabolized by kidney, measurements in renal failure may be inaccurate.[45]

URIC ACID (UA)

- UA in human beings is the final breakdown product of purine metabolism.
- Approximately 2/3rd to 3/4th of urate (ionized form of UA) is excreted via kidneys, and the remaining through the intestines. [46]
- It has a good antioxidant capacity owing to the presence of double bonds, and can serve as an antioxidant for 2/3 of total plasma.[47]
- On account of its elevated dissociation constant (since UA = weak acid), it is present in plasma primarily (98%) as a monovalent salt of sodium (i.e. as urate).
- As a consequence of its low solubility, it is bound to albumin in the plasma, which increases its solubility by almost 70%.
- UA in human blood is almost 50 times more than other mammals (where UA is further catalyzed by urate oxidase or uricase to allantoin).[48]

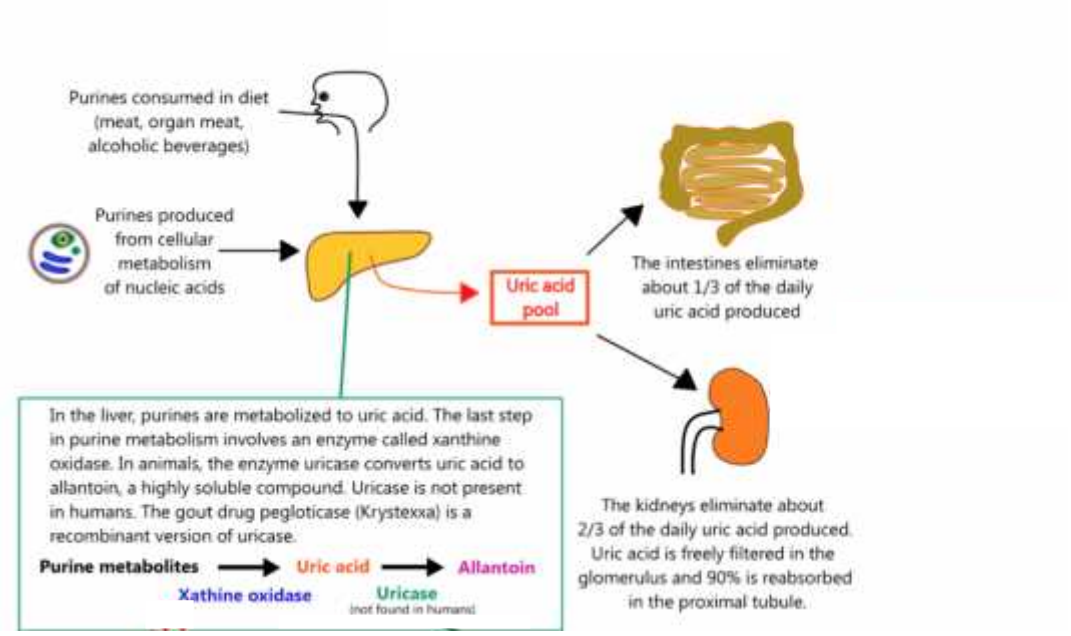


Figure 9 – Uric Acid Homeostasis

In kidney –

- UA and urate- filtered and secreted.
- But majority, i.e. 90% - reabsorbed
- Serum levels are largely regulated by the following urate transporters:
  - reabsorptive transporters - URAT1
    - GLUT9
  - secretory transporters - members of OAT family
    - ABCG2 (intestinal epithelium aso expresses it)
  - ABCG2 dysfunction in an important genetic factor in pathogenesis of elevated SUA levels. [49]

Determinants of increased SUA-

Elevated SUA can result as a result of –

- Increased production :
  - Diet (purine rich)
  - Purine metabolism error e.g. HPRT deficiency, PRPP synthetase over activity
  - Elevated cell turnover – e.g. –tumors, hemolysis, pagets disease etc.
- Decreased excretion – e.g. : kidney dysfunction, drug/toxin induced, sarcoidosis etc. [50]

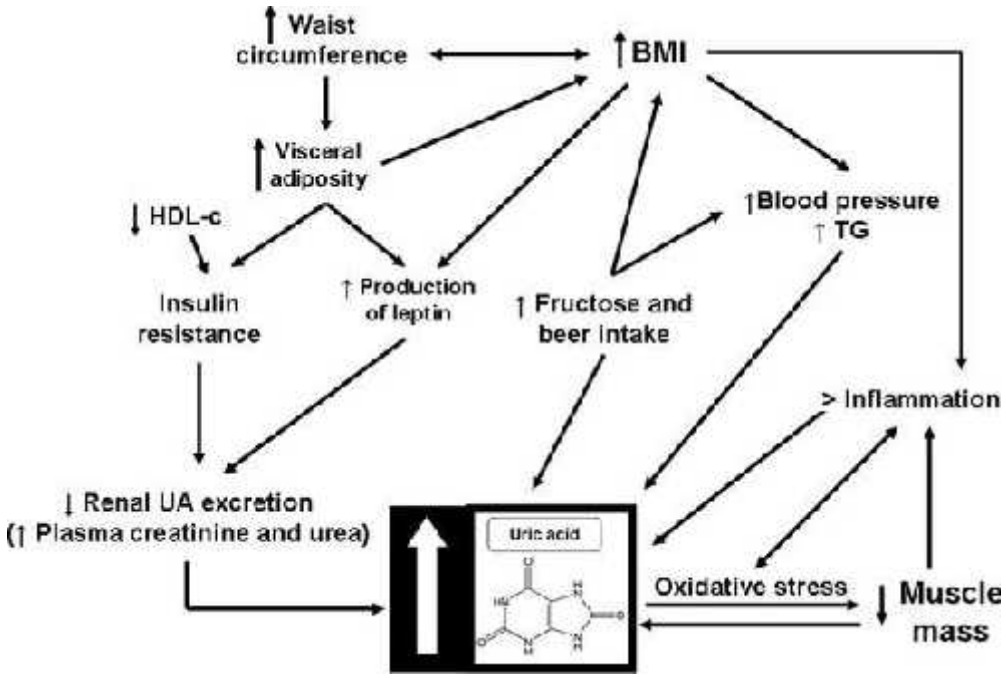


Figure 10 – SUA determinants

Protective effects of UA-

- Acute rise in SUA – antioxidant properties
- Stabilizing actions in Vitamin C and E
- Protective against development of parkinsons and multiple sclerosis.[51,52]

<u>UA as a risk factor for –</u>

- Gouty arthritis
- Renal calculi
- T2DM
- HTN
- Coronary artery disease
- Metabolic syndrome [53,54,55]

UA acts like hydrophobic pro-oxidant intracellularlywhere as like hydrophilic antioxidant extracellularly.

The intracellular pro oxidant effect is because of the following reasons –

- Oxidative stress as a result of super oxide ion generated when xanthine is converted into UA
- Decreased NO synthesis, causing eNOS dysfunction
- Increased inflammation [56]

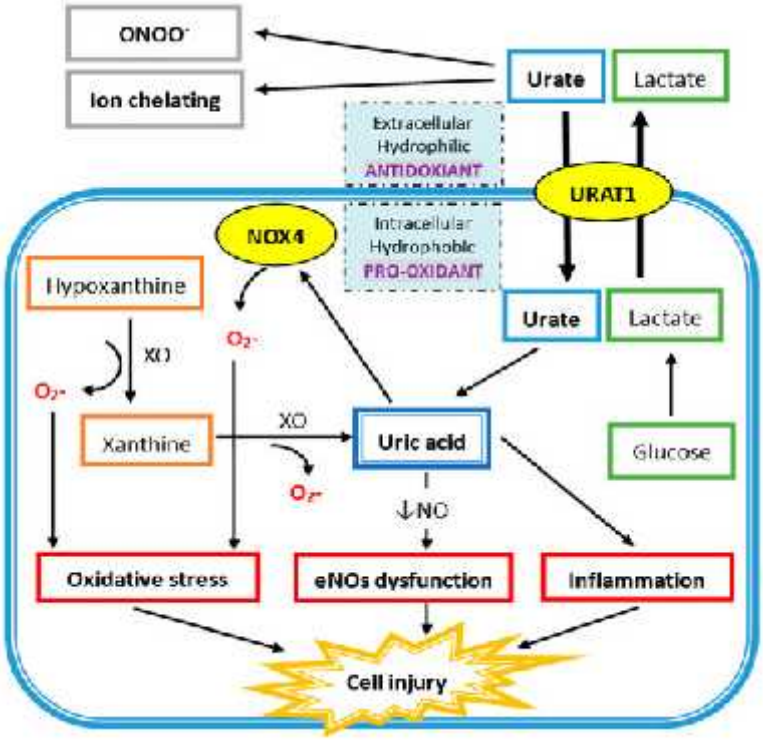


Figure 11 – UA oxidant-anti oxidant paradox

UA and T2DM

- Several studies have established the association of high UA with various diseases including metabolic disorders, gout, hypertension, atherosclerosis, renal diseases, etc.

- The association between SUA and impaired glucose homeostasis was first described in 1923.

- Later in 1950s, it was noticed that DM and gout often co-exist. [57,58]

- Initial studies had shown the role of uric acid in type 2 diabetes mellitus as a bystander role which was explained by the following two reasons – first, hyperinsulinemia may decrease the renal excretion of uric acid, thus increasing the serum levels of the same, and second, increased oxidative stress as a result of sub clinical chronic inflammation preceding the development of diabetes mellitus, resulting in increased serum levels of UA. [59, 60, 61]

- Since last 2 decades, it's been hypothesised in several studies that high SUA may be a potential precursor for the development of DM rather than just a consequence of IR, i.e. causal role. [62]

- Multiple meta-analyses have reported that with every 1mg/dl increase in SUA level, there is an approximate 6-20 % increased risk of development of type 2 diabetes mellitus. [63]

- Studies have suggested that elevated levels of UA can cause pancreatic β cell injury via activation of the "NF-κB-NOS-NO" signal axis. Excessive nitric oxide (NO) synthesis is an important mechanism causing apoptotic damage to the pancreatic beta cells. Inducible NO synthase (iNOS) is one of the downstream targets of the NF-κB pathway. [64]
- Thus to summarize ,

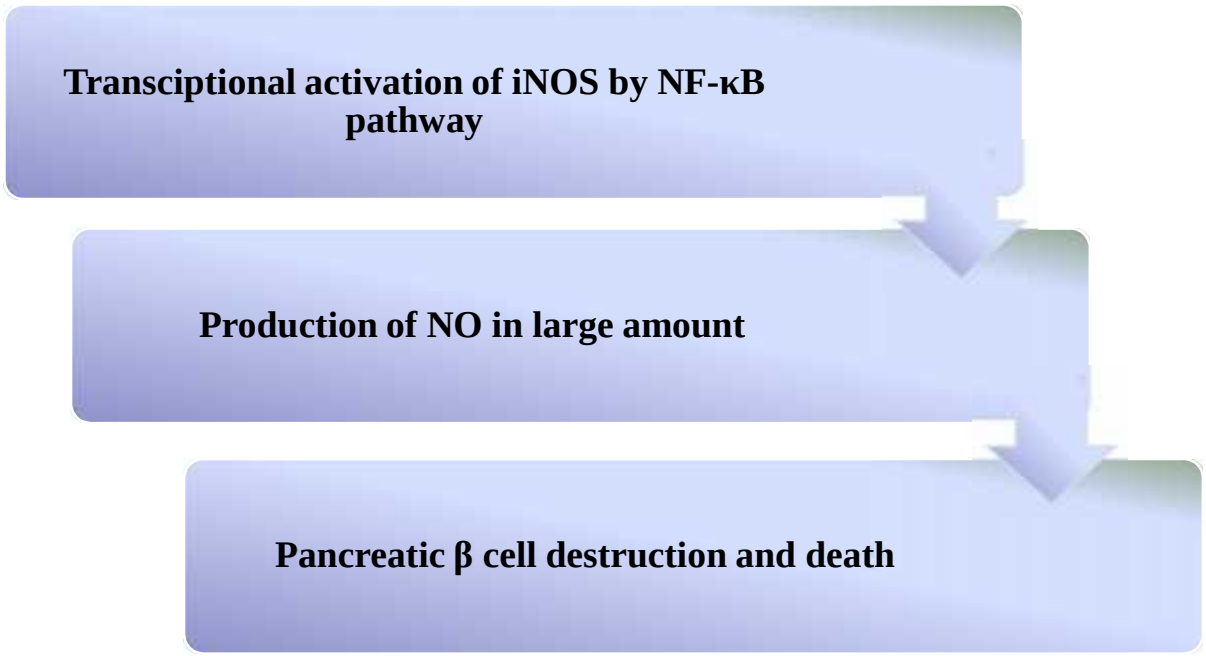


Figure 12 - "NF-κB-NOS-NO" signal axis

- Another mechanism by which high uric acid causes decreased insulin production by β pancreatic cells is by "ROS–AMPK–ERK" signalling pathway. [65]

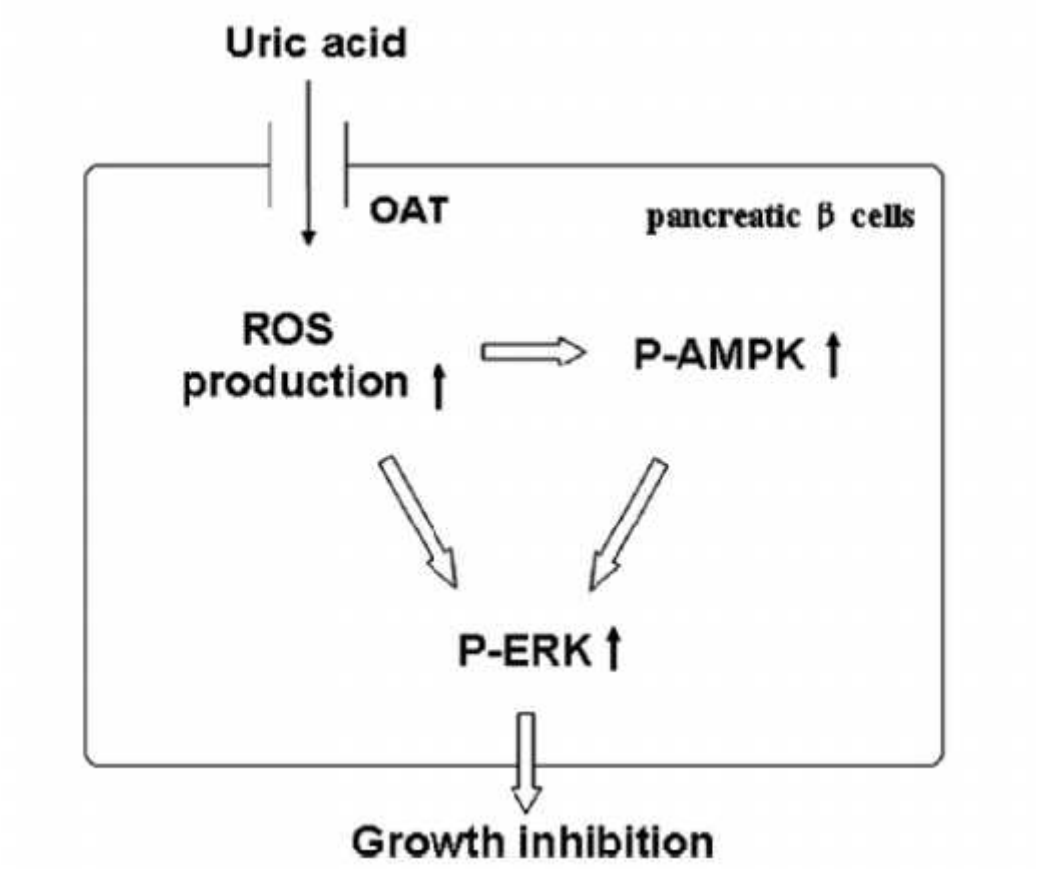


Figure 13 –Mechanism of UA-induced oxidative stress and growth inhibition in pancreatic β cells

As shown in the figure,

- UA enters the pancreatic β cell by organic anion transporter (OAT).
- Once inside the cell,UA rapidly induce oxidative stress by reactive oxygen species (ROS).
- This in turn activates the AMPK and ERK signalling pathways.
- UA activated ERK phosphorylation plays an important role in growth inhibition of pancreatic β cells and consequently decreased insulin secretion.[66]

Richard J. Johnson et al. in his study between UA and DM deduced a causal relationship between the two by adapting the Koch's postulates, as shown in the table. [67]

1. An elevated serum uric acid predicts the development of diabetes (epidemiology).
2. Experimentally raising uric acid with fructose causes insulin resistance in rats.
3. Lowering serum uric acid improves insulin resistance in fructose-dependent and -independent models of metabolic syndrome.
4. Cellular mechanisms by which uric acid can induce diabetes have been identified.
5. A pilot study reported that lowering serum uric acid improves insulin resistance in subjects with hyperuricemia but this was not shown in subjects administered high doses of fructose.

Table 8 - Koch's postulates adapted to SUA & DM

METHODOLOGY

The current study was carried out in the Medicine dept., KLES Dr. PK Hospital & MRC, Belagavi from the month of January to December 2019.

Study design

The study design was a hospital based observational cross sectional study.

Study period

The present study was done for the period of one year from January 2019 to December 2019.

Place

Medicine dept., KLES Dr. PK Hospital & MRC, Belagavi, a tertiary care teaching hospital attached to Jawaharlal Nehru College, Belagavi.

Source of Data

Newly diagnosed T2DM patients admitted to KLES Dr. PK Hospital & MRC, Belagavi.

Sample size

76 patients with newly diagnosed T2DMstudied.

Sampling procedure

The sample size was calculated using the following formula –

Sample size (n) = $4PQ/D^2$

Where,

n = Sample size

P = Prevalence of the disease

Q = (100-P)

D = The precision of the estimate

4 derived from square of Z (95% CI =1.96)

Here, P = 5

Q = 95

D = 5

Therefore, $n = (4 \times 5 \times 95)/ 5^2$

n = 76

Hence the sample size of 76 was considered for this study.

Sample Method

Convenient sampling method - All patients attaining selection criteria were encompassed.

Selection criteria

Inclusion Criteria

- Patients ≥18 yrs who have been newly diagnosed as T2DM using the ADA criteria.

.

Exclusion Criteria

- Patients with diabetic micro and macro-vascular complications
- Thyroid disease

- Cushing syndrome
- Liver cirrhosis
- Pheochromocytoma
- Renal failure (Serum Creatinine > 1.5 mgdl)
- Malignant tumors
- Those who are currently taking UA-lowering therapy

Ethical clearance

Prior to the beginning, the study was approved by the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi.

Informed consent

The patients who fulfilled the selection criteria were informed about the nature of the study and a written informed consent was obtained (Annexure-I).

Data Collection

The selected patients were interviewed for the history of presenting illness and other co morbid conditions and the demographic data. Following this detailed clinical as well as systemic examination was carried out. Patients were evaluated for the following parameters –

- BMI - computed as

$$BMI = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

- BP – determined using sphygmomanometer.
- Fundus examination was done by a fundoscope.

A preformulated proforma was constructed and all the relevant data was noted(Annexure – II).

Investigations

5 ml plain venous blood sample after overnight fasting and 5 ml plain venous blood sample 2 hours postprandial were obtained from the selected patients by venepuncture and were processed immediately for the following investigations.

- Fasting and Post prandial blood sugars
- Serum Uric acid
- Fasting C peptide or Fasting serum insulin level
- Glycosylated Haemoglobin (HbA1C)
- Serum creatinine

All parameters were analyzed by available standardized enzymatic methods.

Islet β cell function index

HOMA-IR was calculated in order to assess IR, and thus the pancreatic islet β cell function.

Values of fasting blood glucose and either fasting C-peptide or fasting serum insulin levels were entered in the HOMA 2 calculator and values of HOMA-IR were obtained.

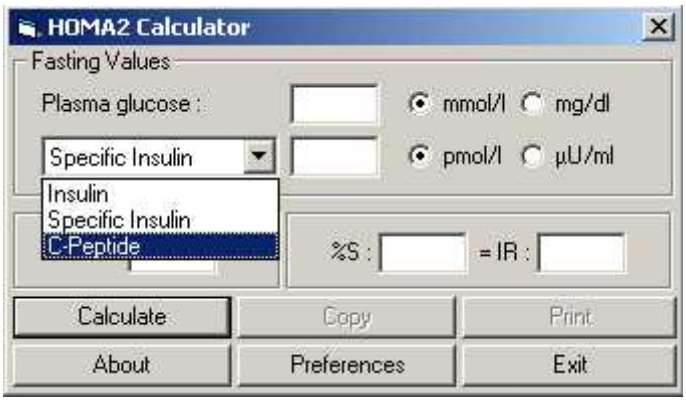


Figure 14 – HOMA-IR Calculator

STATISTICAL METHODS

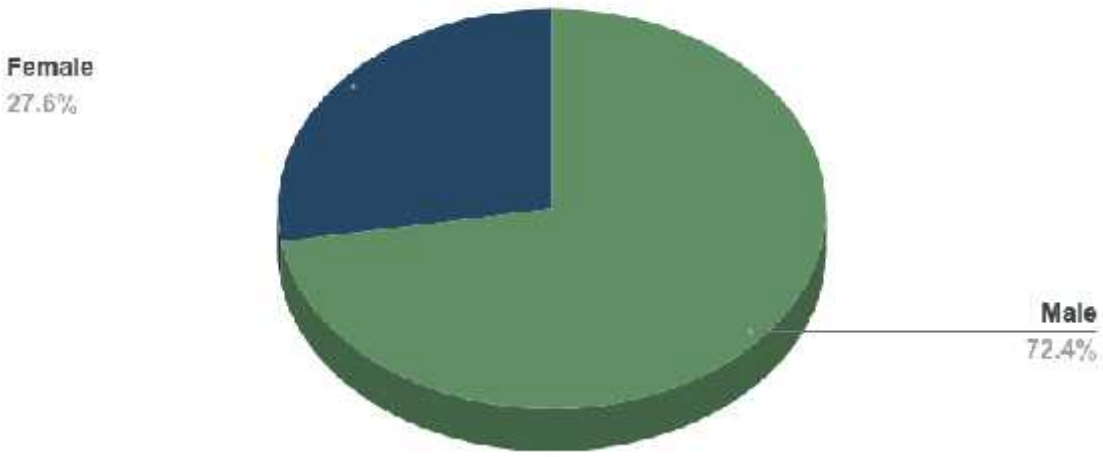
The data obtained was coded and entered into Microsoft excel spreadsheet and data was analyzed using SPSS version 21. The categorical data was expressed in terms of rates, ratios and percentages and the continuous data wasexpressed in terms of mean ± standard deviation. The association between the clinical and demographic characteristics were tested using chi square test where as t test and one way ANOVA test were applied for group-comparison of the skewed data. The correlation of serum uric acid with islet β cell function was determined using Karl Pearson's correlation coefficient method. At 95% confidence interval, a probability (p) value of ≤ 0.050 was considered as statistically significant. Multiple linear regression analysis of HOMA-IR scores by other variables was carried out.

RESULTS

Table 9 : Distribution of the study population according to sex.

SEX	NUMBER	PERCENTAGE
Male	55	72.4
Female	21	27.6
Total	76	100.00

Graph 1 : Distribution of the study population according to sex.

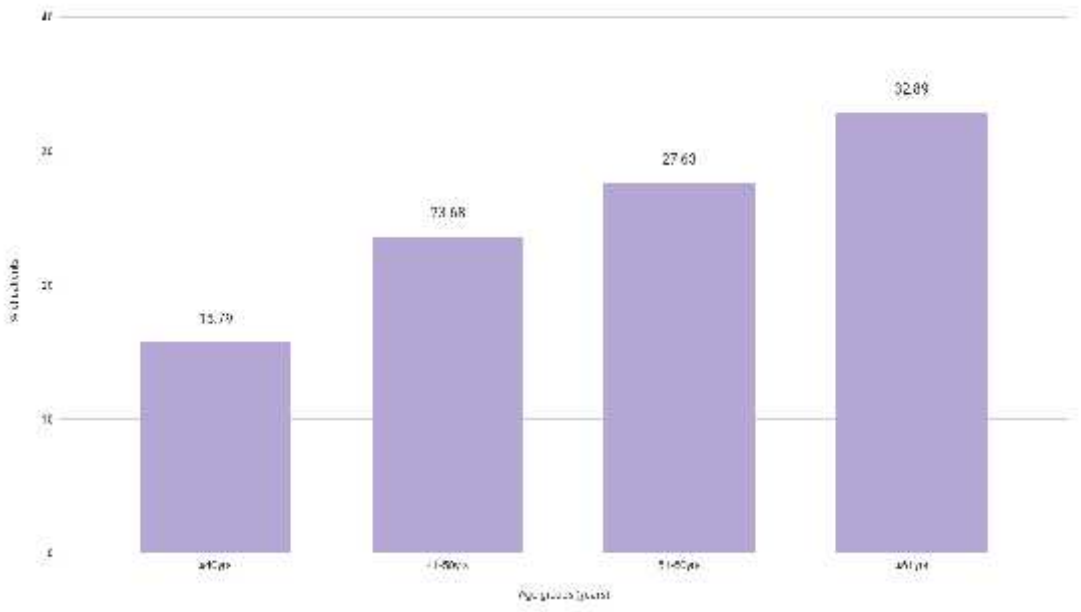


In this study, 72.4% of the patients were male and 27.6% were female. The male to female ratio was 2.62 : 1.

Table 10 : Distribution of the study population according to the age.

AGE GROUPS	NUMBER	PERCENTAGE
≤40yrs	12	15.79
41-50yrs	18	23.68
51-60yrs	21	27.63
≥61yrs	25	32.89
Total	76	100.00
Mean age	53.76	
SD age	13.33	

Graph 2 : Distribution of the study population according to the age

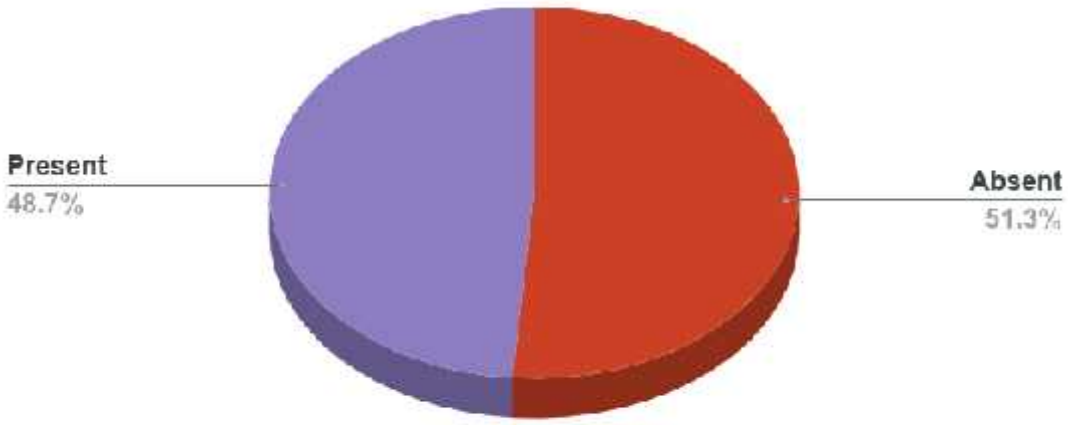


In this study, most of the patients were more than 60 years of age (32.89%). The mean age was 53.76 ± 13.33years, with range being between 20 and 84 years.

Table 11 : Distribution of study population according to the prevalence of Hypertension

HYPERTENSION	NUMBER	PERCENTAGE
Absent	39	51.3
Present	37	48.7
Total	76	100.00

Graph 3 : Distribution of study population according to the prevalence of Hypertension

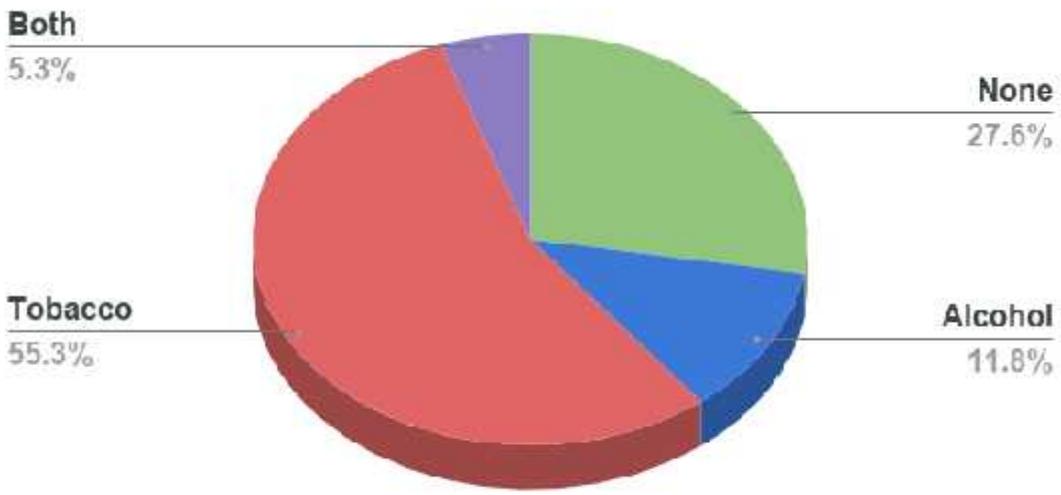


In the present study, 48.7 % of the patients had associated hypertension.

Table 12 : Distribution of study population according to the habits

HABITS	NUMBER	PERCENTAGE
None	21	27.6
Alcohol	9	11.8
Tobacco	42	55.3
Both	4	5.3
Total	76	100.00

Graph 4 : Distribution of study population according to the habits

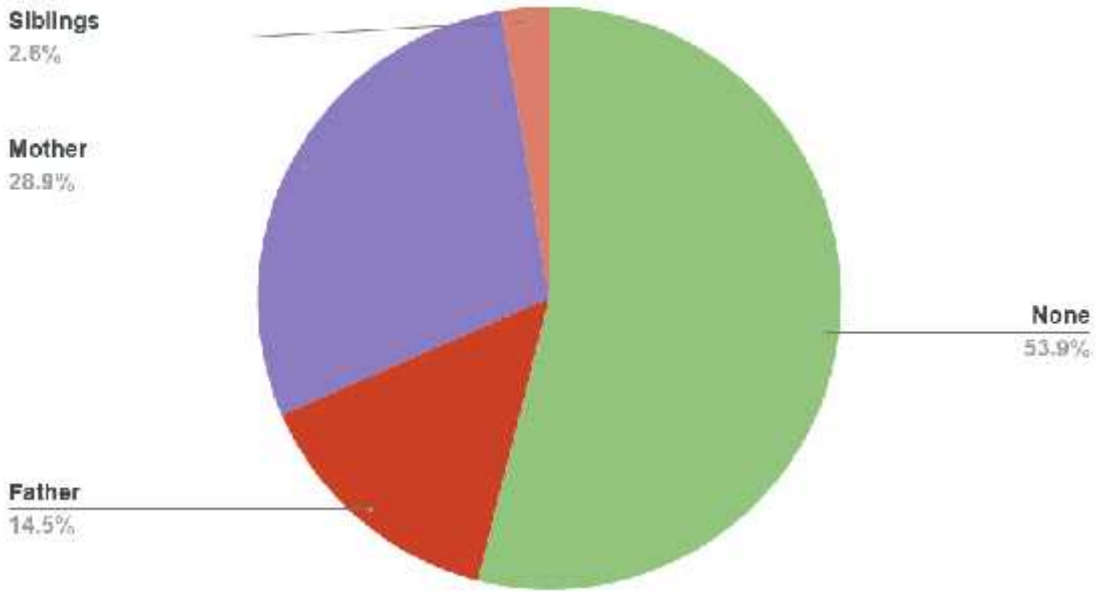


In the present study, the most common habit was tobacco consumption (55.3% of the patients).

Table 13 : Distribution of study population according to the family history of diabetes mellitus

FAMILY HISTORY	NUMBER	PERCENTAGE
None	41	53.9
Father	11	14.5
Mother	22	28.9
Siblings	2	2.6
Total	76	100.00

Graph 5 : Distribution of study population according to the family history of diabetes mellitus

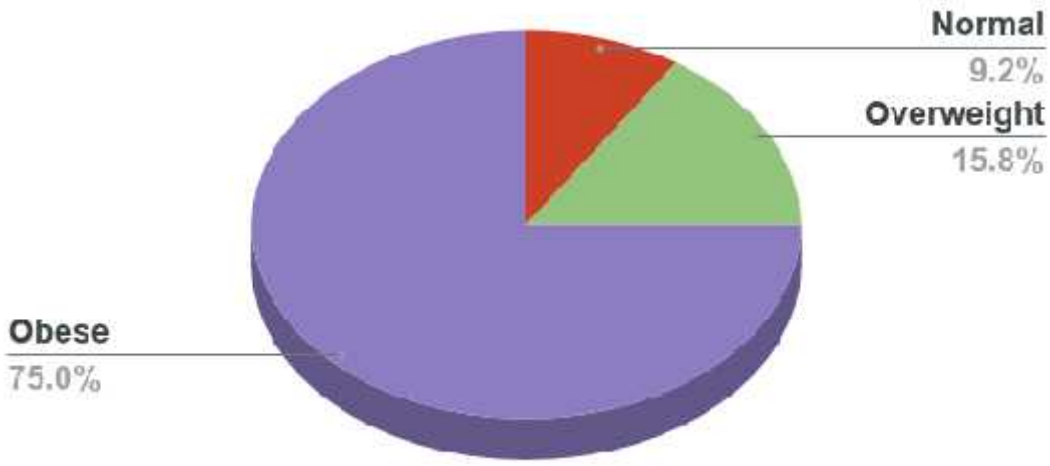


In this study, family history of diabetes mellitus was present in 46.1 % of the study population.

Table 14 : Distribution of study population according to the BMI

Obesity	NUMBER	PERCENTAGE
Normal	7	9.2
Overweight	12	15.8
Obese	57	75.0
Total	76	100.0
Mean BMI	27.19	
SD BMI	3.23	

Graph 6 : Distribution of study population according to the BMI



In the present study, most of the patients were obese (75 %), i.e. ≥25 kg/m^2 . The mean BMI of the study population was 27.19 ± 3.23 kg/m^2.

Table 15 : Distribution of study population according to the signs of Insulin Resistance

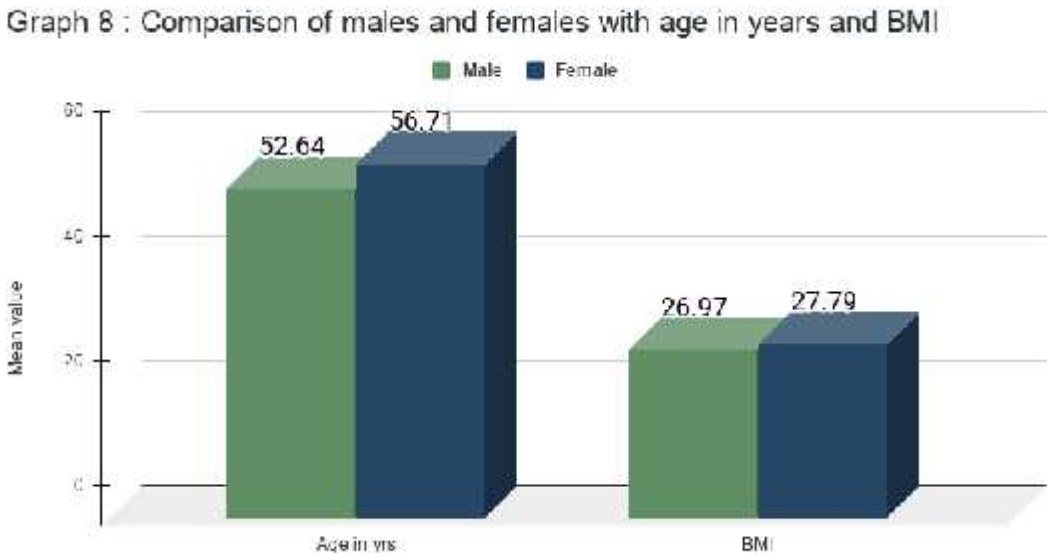
Insulin Resistance signs	NUMBER	PERCENTAGE
Absent	39	51.3
Present	37	48.7
Total	76	100.0

Graph 7 : Distribution of study population according to the signs of Insulin Resistance

In the present study, 48.7 % of the patients had signs of insulin resistance on physical examination.

Table 16: Comparison of males and females with age in years and BMI scores by t test

Parameters	Male		Female		t-value	p-value
	Mean	Std.Dev.	Mean	Std.Dev.		
Age in yrs	52.64	11.83	56.71	16.62	-1.1956	0.2357
BMI(kg/m^2)	26.97	3.27	27.79	3.13	-0.9864	0.3271



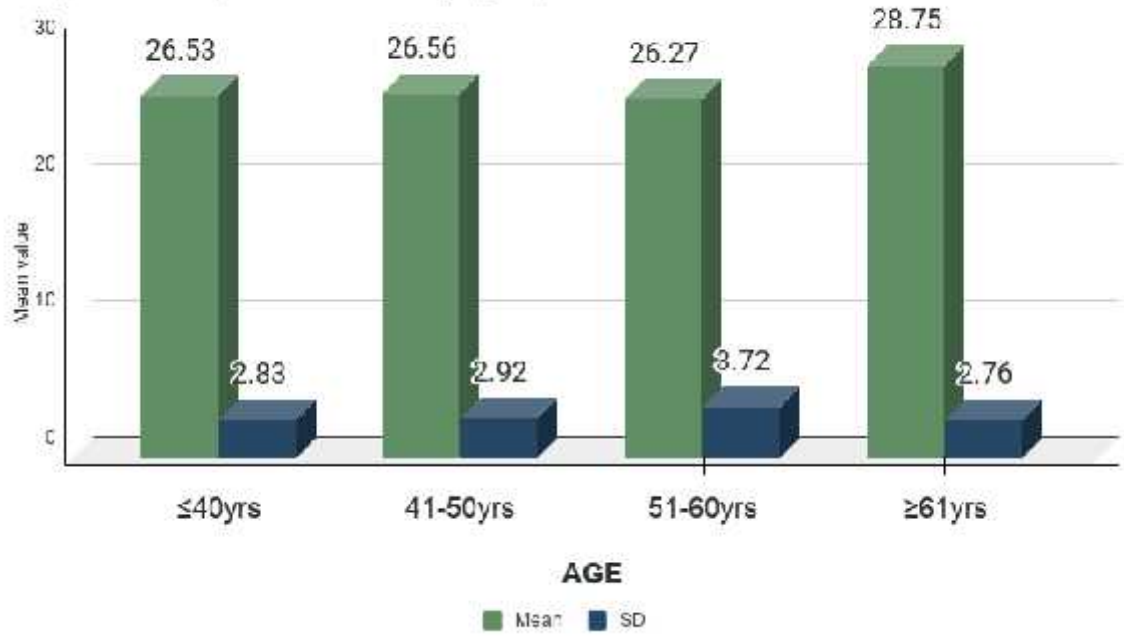
In the present study, among the male patients, mean age was 52.64 ± 11.83 years and mean BMI was 26.97 ± 3.27 kg/m^2. Similarly, among the female patients, mean age was 56.71 ± 16.62 years and mean BMI was 27.79 ± 3.13 kg/m^2 .

Table 17 : Comparison of the age groups with BMI by one way ANOVA

Summery	≤40yrs	41-50yrs	51-60yrs	≥61yrs	Total	F-value	P-value
Mean (kg/m^2)	26.53	26.56	26.27	28.75	27.19	3.1502	0.0301*
SD	2.83	2.92	3.72	2.76	3.23		

*p<0.05

Graph 9 : Comparison of the age groups with BMI

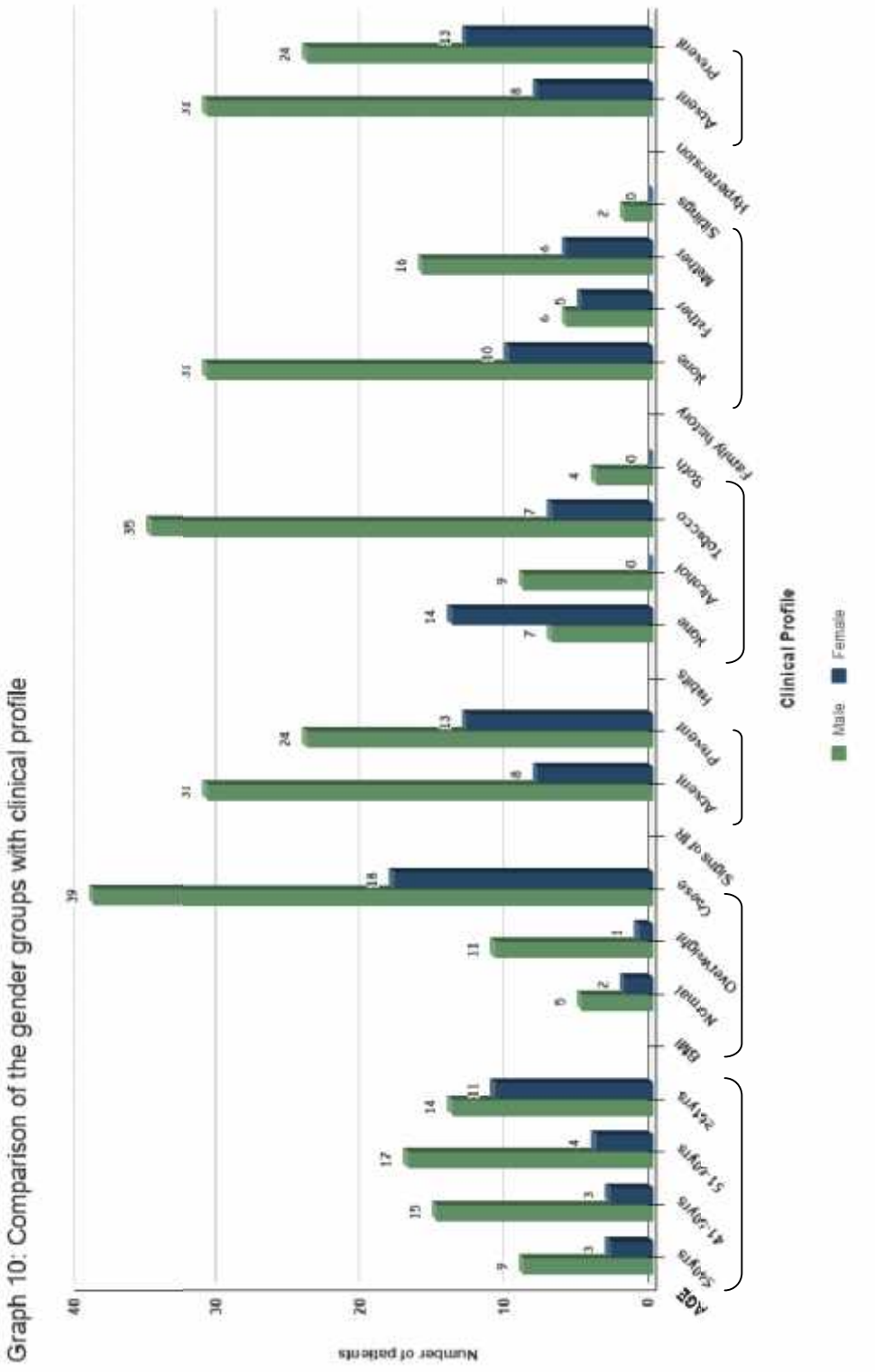


In the present study, the maximum BMI was observed in the patients of age group ≥61years, with a mean BMI of 28.75 ± 2.76 kg/m^2 in that age group. Mean BMI of other age groups are shown in graph 9.

Table 18: Comparison of the gender groups with clinical profile

	Male	%	Female	%	Total	%	χ^2	p-value
Age groups							5.2473	0.1546
≤40yrs	9	16.36	3	14.29	12	15.79		
41-50yrs	15	27.27	3	14.29	18	23.68		
51-60yrs	17	30.91	4	19.05	21	27.63		
≥61yrs	14	25.45	11	52.38	25	32.89		
BMI							5.2473	0.1546
Normal	5	9.09	2	9.52	7	9.21		
Overweight	11	20.00	1	4.76	12	15.79		
Obese	39	70.91	18	85.71	57	75.00		
Status of signs of IR							2.0302	0.1542
Absent	31	56.36	8	38.10	39	51.32		
Present	24	43.64	13	61.90	37	48.68		
Habits							23.4909	0.0001*
None	7	12.73	14	66.67	21	27.63		
Alcohol	9	16.36	0	0.00	9	11.84		
Tobacco	35	63.64	7	33.33	42	55.26		
Both	4	7.27	0	0.00	4	5.26		
Family history							2.7279	0.4355
None	31	56.36	10	47.62	41	53.95		
Father	6	10.91	5	23.81	11	14.47		
Mother	16	29.09	6	28.57	22	28.95		
Siblings	2	3.64	0	0.00	2	2.63		
Hypertension							2.0302	0.1542
Absent	31	56.36	8	38.10	39	51.32		
Present	24	43.64	13	61.90	37	48.68		
Total	55	100.00	21	100.00	76	100.00		

*$p<0.05$



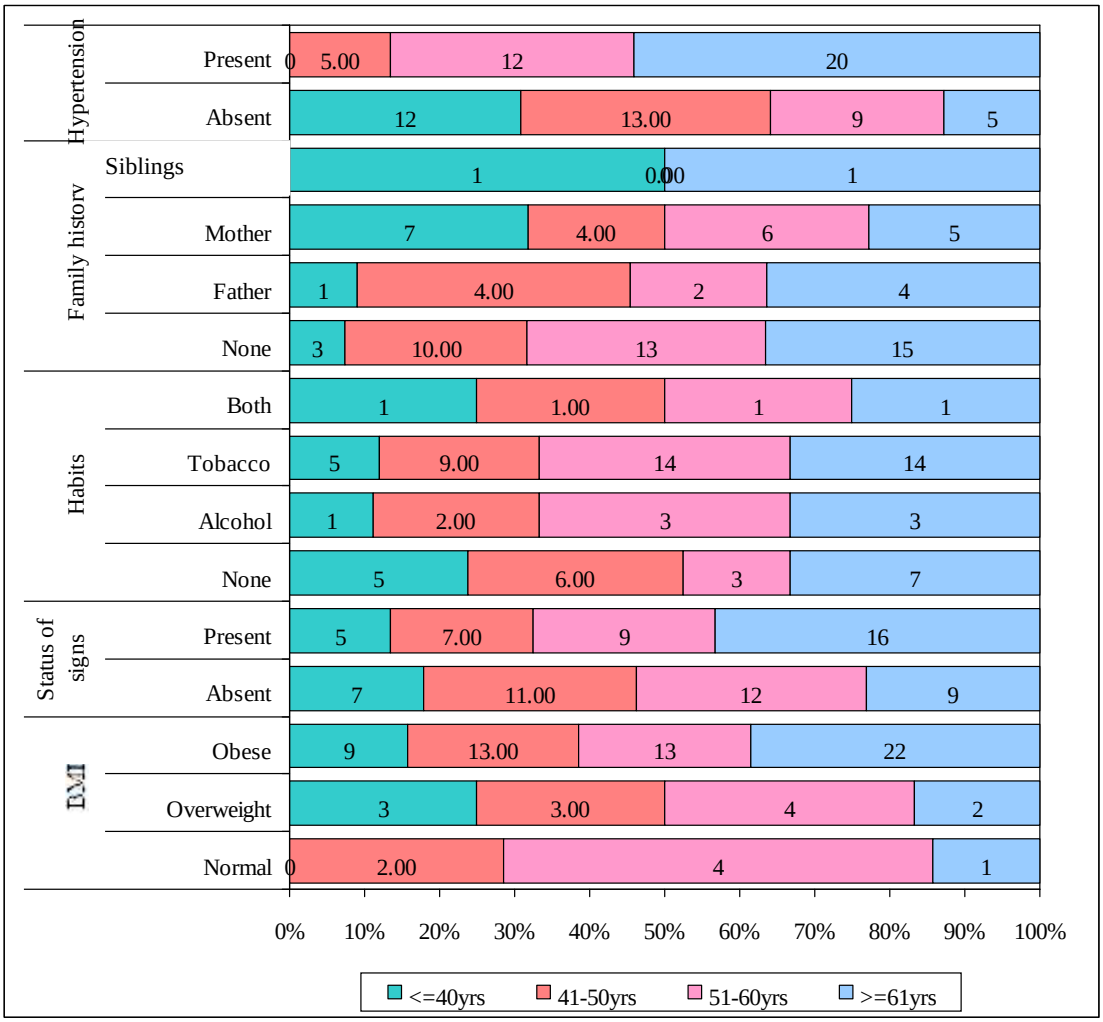
The clinical profile of the study population in the present study compared on the basis of gender distribution is shown in table 18.

Table 19: Comparison of age groups with clinical profile (numbers are in %)

	<=40yrs	41-50yrs	51-60yrs	>=61yrs	Total	χ^2	p-value
BMI						6.9365	0.3268
Normal	0.00	28.57	57.14	14.29	7		
Overweight	25.00	25.00	33.33	16.67	12		
Obese	15.79	22.81	22.81	38.60	57		
Status of signs						3.5606	0.3130
Absent	17.95	28.21	30.77	23.08	39		
Present	13.51	18.92	24.32	43.24	37		
Habits						3.9533	0.9145
None	23.81	28.57	14.29	33.33	21		
Alcohol	11.11	22.22	33.33	33.33	9		
Tobacco	11.90	21.43	33.33	33.33	42		
Both	25.00	25.00	25.00	25.00	4		
Family history						10.9839	0.2769
None	7.32	24.39	31.71	36.59	41		
Father	9.09	36.36	18.18	36.36	11		
Mother	31.82	18.18	27.27	22.73	22		
Siblings	50.00	0.00	0.00	50.00	2		
Hypertension						24.9488	0.0001*
Absent	30.77	33.33	23.08	12.82	39		
Present	0.00	13.51	32.43	54.05	37		
Total	15.79	23.68	27.63	32.89	76		

*$p<0.05$

Graph 11: Comparison of the age groups with clinical profile



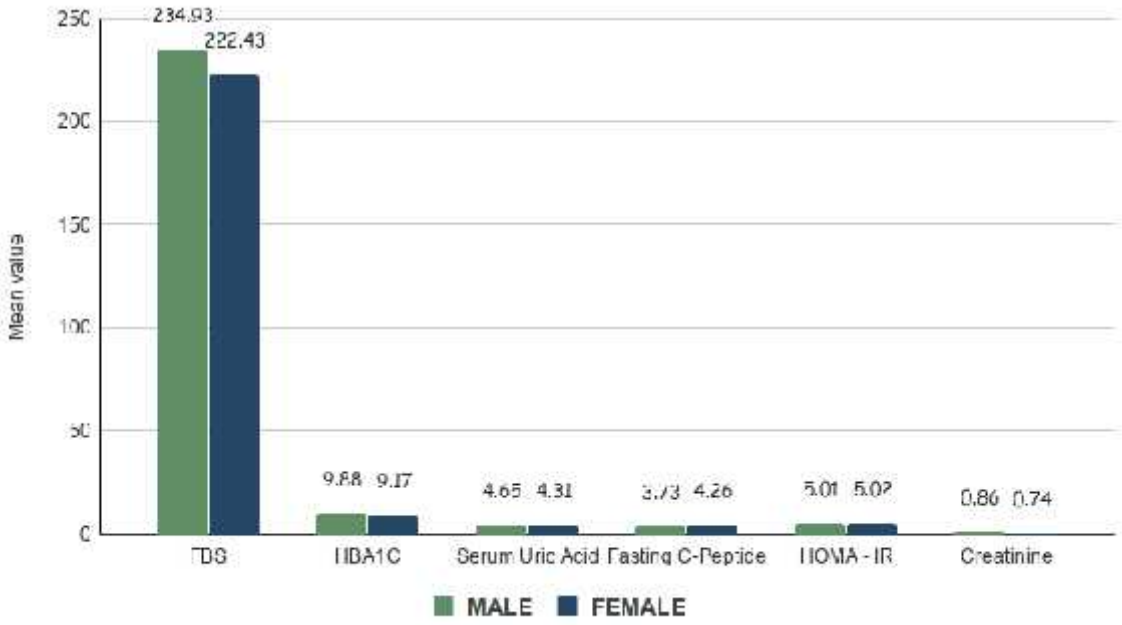
The clinical profile of the study population in the present study compared on the basis of age distribution is shown in table 19.

Table 20 : Comparison of the gender groups with clinical parameters by t test

Parameters	Male		Female		t-value	p-value
	Mean	Std.Dev.	Mean	Std.Dev.		
FBS	234.93	67.52	222.43	64.21	0.7312	0.4670
HBA1C	9.88	2.67	9.17	2.98	1.0046	0.3184
Serum Uric Acid	4.65	1.81	4.31	1.94	0.7117	0.4789
Fasting c-peptide	3.73	2.55	4.26	2.36	-0.8154	0.4175
HOMA – IR	5.01	7.44	5.02	4.63	-0.0058	0.9954
Creatinine	0.86	0.20	0.74	0.32	2.1052	0.0387*

*p<0.05

Graph 12 : Comparison of the gender groups with clinical parameters

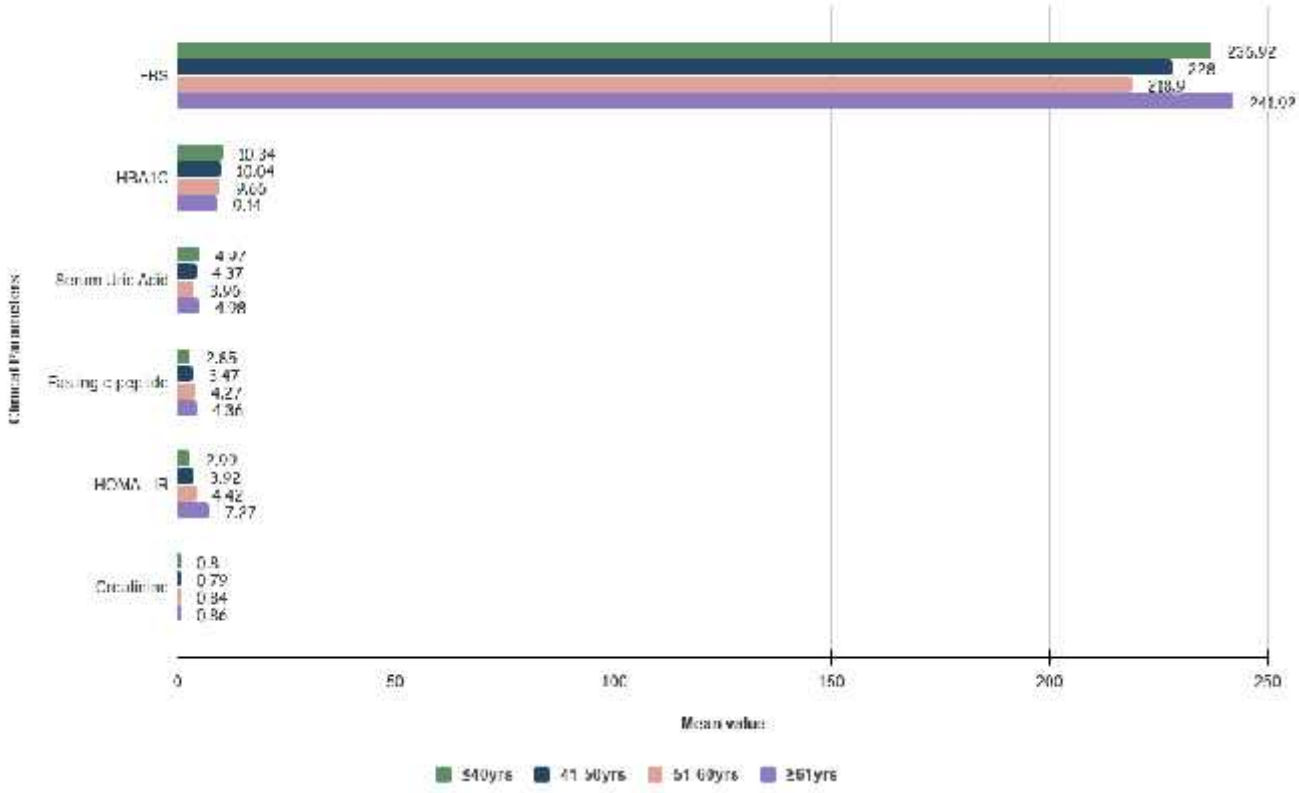


The clinical parameters of the study population in the present study compared on the basis of gender distribution is shown in table 20.

Table 21: Comparison of the age group with clinical parameters by one way ANOVA

Parameters		≤40yrs	41-50yrs	51-60yrs	≥61yrs	Total	F-value	p-value
FBS	Mean	236.92	228.00	218.90	241.92	231.47	0.4897	0.6905
	SD	53.66	61.35	66.95	76.12	66.43		
HBA1C	Mean	10.34	10.04	9.66	9.14	9.69	0.6509	0.5849
	SD	3.83	2.22	2.92	2.41	2.76		
Serum Uric Acid	Mean	4.97	4.37	3.96	4.98	4.55	1.4601	0.2326
	SD	2.29	1.53	1.19	2.19	1.84		
Fasting c-peptide	Mean	2.85	3.47	4.27	4.36	3.88	1.3260	0.2727
	SD	2.23	2.21	3.04	2.21	2.49		
HOMA – IR	Mean	2.99	3.92	4.42	7.27	5.01	1.5347	0.2129
	SD	2.09	2.76	3.20	10.86	6.75		
Creatinine	Mean	0.80	0.79	0.84	0.86	0.83	0.3553	0.7855
	SD	0.23	0.18	0.19	0.32	0.24		

Graph 13 : Comparison of the age groups with clinical parameters



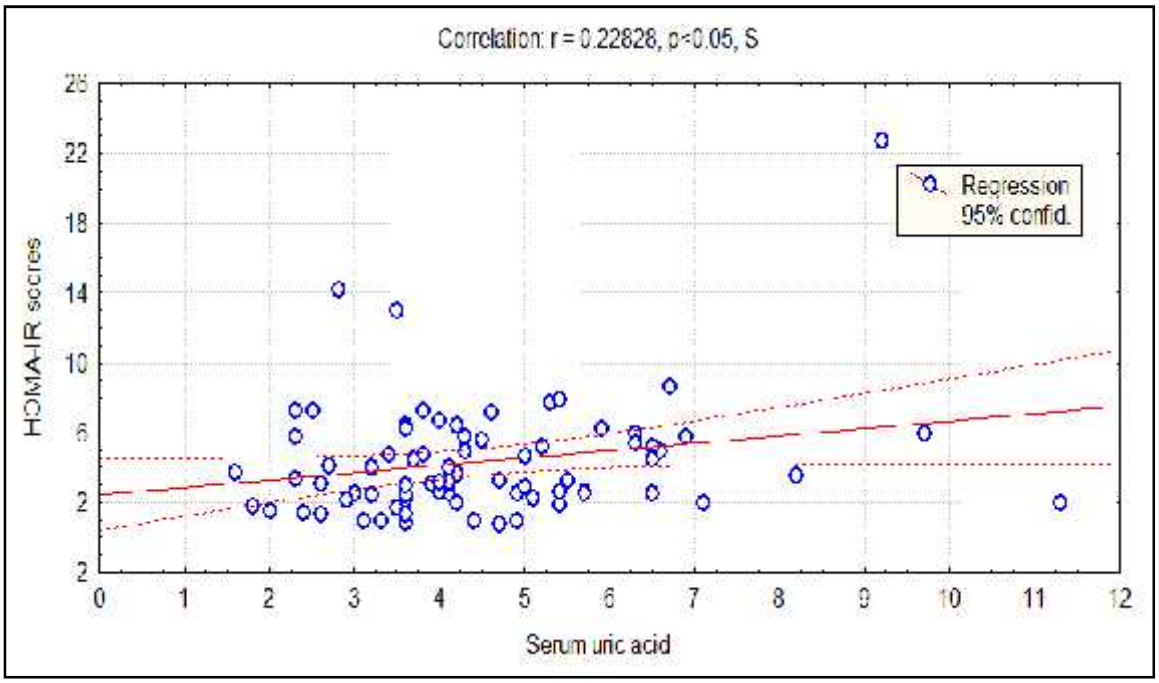
The clinical parameters of the study population in the present study compared on the basis of age distribution is shown in table 21.

Table 22: Correlation between Serum uric acid levels and HOMA-IR by Karl Pearson's correlation coefficient method

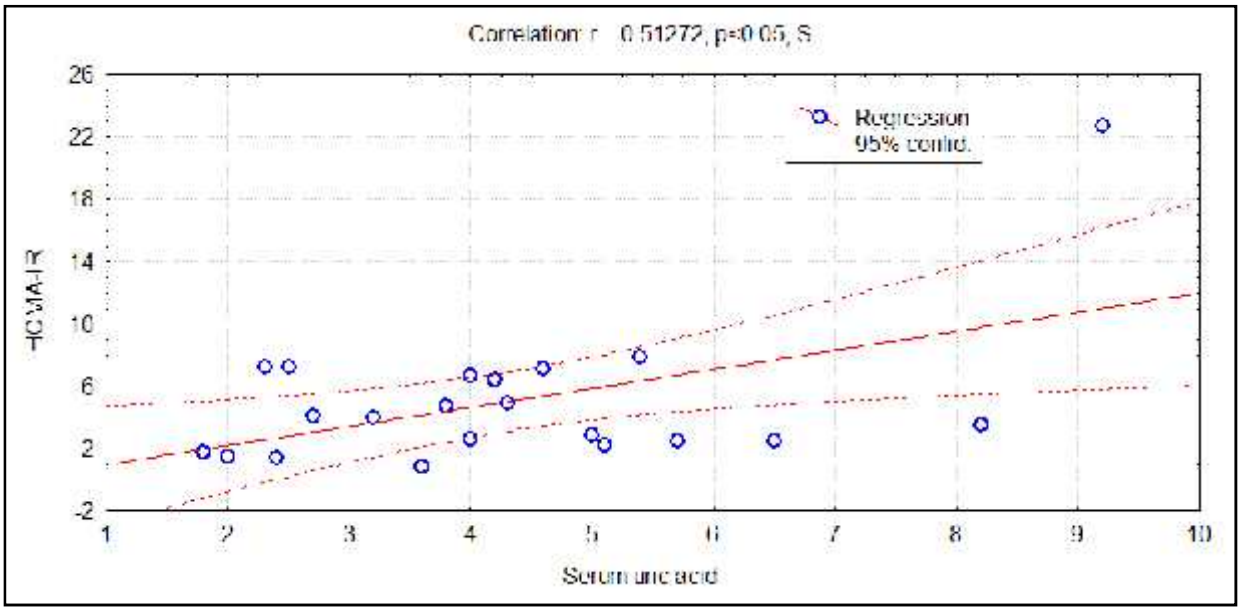
Samples	Parameters	Correlation between Serum uric acid with		
		r-value	t-value	p-value
Total	HOMA-IR	0.2283	2.0033	0.0489*
Males	HOMA-IR	0.0549	0.3965	0.6933
Females	HOMA-IR	0.5127	2.6031	0.0175*

*p<0.05

Graph 14 : Scatter diagram showing the correlation between Serum uric acid levels and HOMA-IR in total study population



Graph 15 : Scatter diagram showing the correlation between Serum uric acid levels and HOMA-IR in female study population



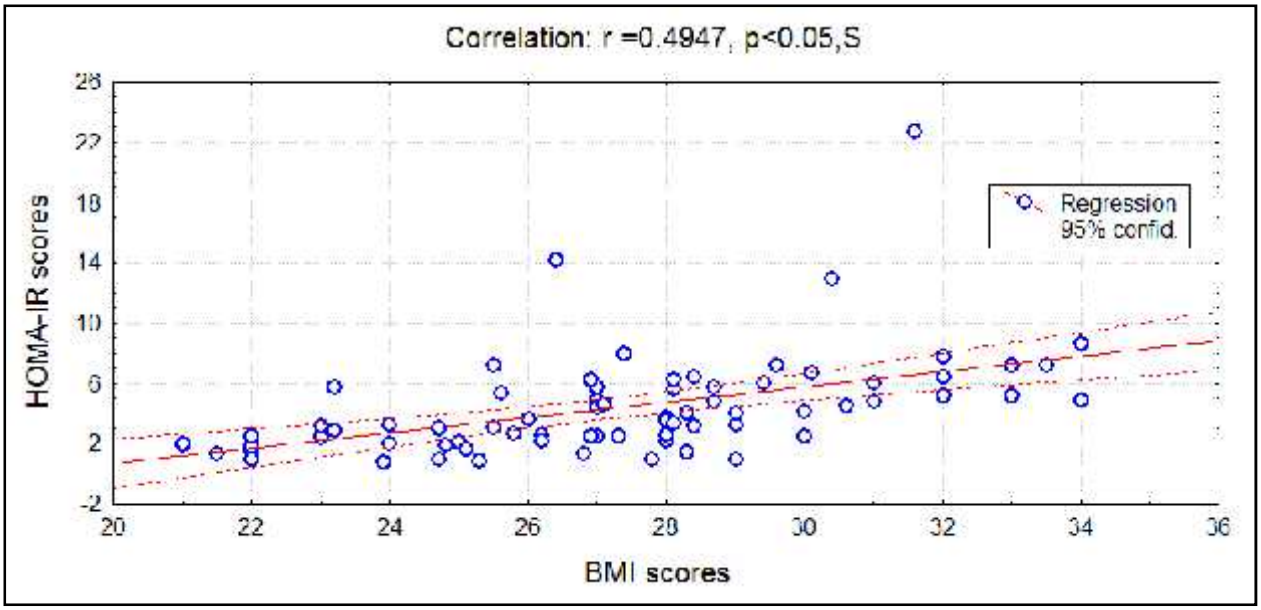
In the present study, a positive and significant correlation was observed between SUA & HOMA-IR (r=0.2283, p=0.0489) at 5% level, when SUA was modelled as a continuous variable .On further gender wise stratification, in the female population SUA and HOMA –IR had a positive and significant correlation (r=0.5127, p=0.0175) at 5% level, where as in the male population the correlation was positive, but not significant (r=0.0549, p=0.6933) at 5% level.

Table 23: Correlation between BMI and HOMA-IR levels by Karl Pearson's correlation coefficient method

Parameters	Correlation between BMI with		
	r-value	t-value	p-value
HOMA-IR	0.4948	4.8644	0.0001*

*p<0.05

Graph 16: Scatter diagram showing the correlation between BMI and HOMA-IR levels

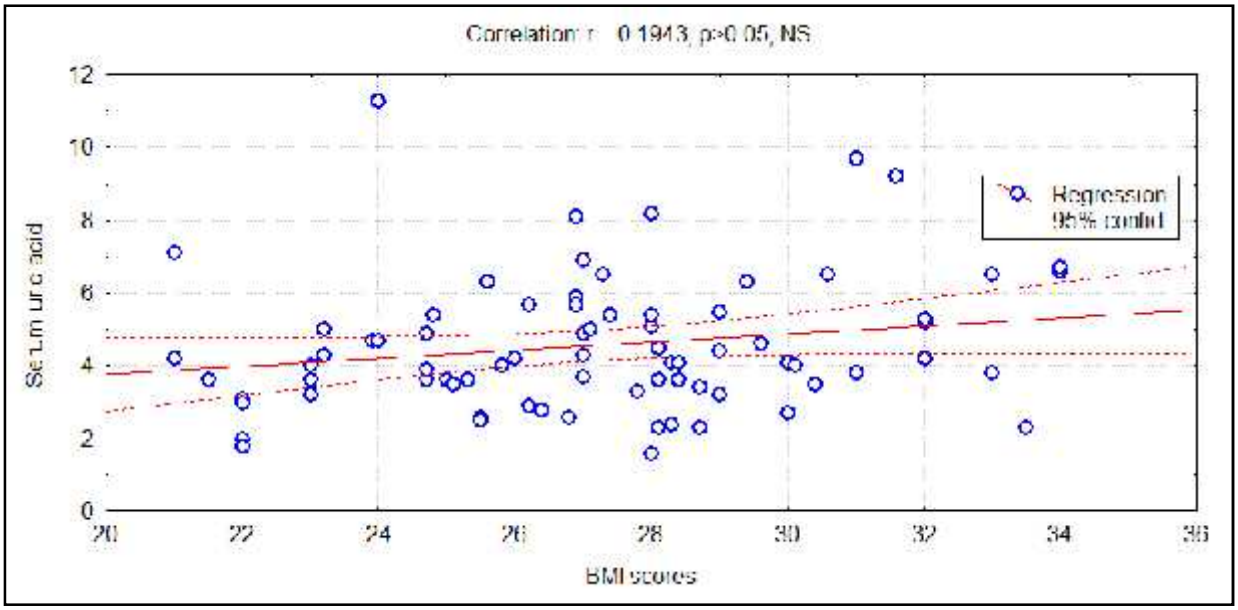


In the present study, positive &significant correlation was found between BMI and HOMA-IR (r=0.4948, p=0.0001)at 5% level.

Table 24: Correlation between BMI and serum uric acid levels by Karl Pearson's correlation coefficient method

Parameters	Correlation between BMI with		
	r-value	t-value	p-value
Serum uric acid	0.1943	1.7043	0.0925

Graph 17 : Scatter diagram showing the correlation between BMI and serum uric acid levels



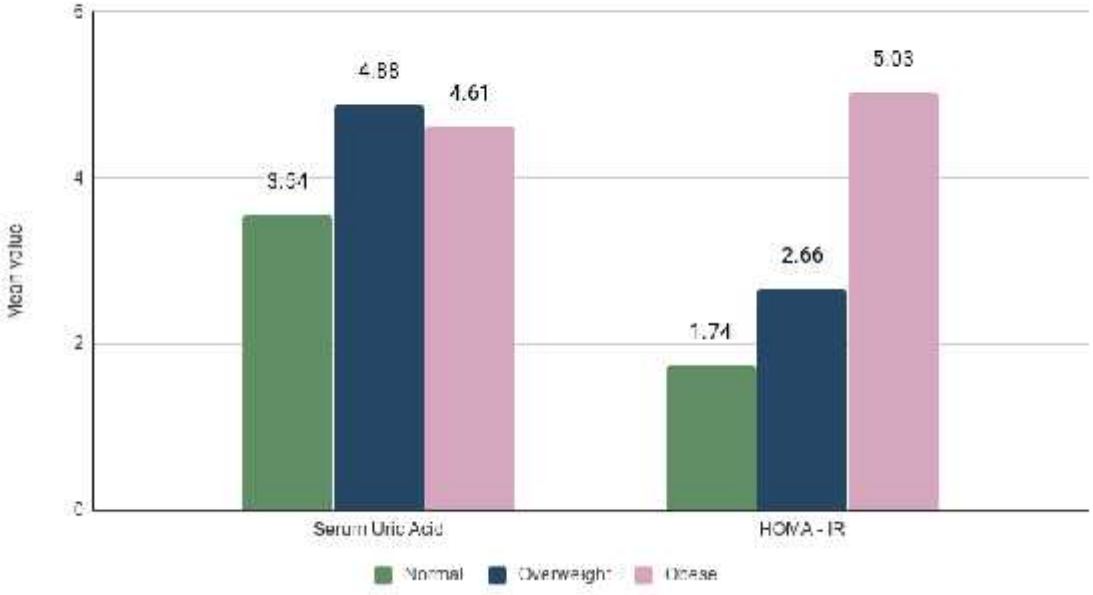
In this study, a positive correlation was noted between BMI and SUA levels which was not statistically significant (r=0.1943, p=0.0925)at 5% level.

Table 25: Comparison of BMI with Serum Uric Acid and HOMA-IR by one way ANOVA

Parameters	Summery	Normal	Overweight	Obese	Total	F-value	p-value
Serum Uric Acid	Mean	3.54	4.88	4.61	4.55	1.2785	0.2846
	SD	1.78	2.13	1.78	1.84		
HOMA – IR	Mean	1.74	2.66	5.03	4.34	5.3880	0.0066*
	SD	0.49	1.28	3.57	3.34		

*p<0.05 (Normal vs obese)

Graph 18 : Comparison of BMI with Serum Uric Acid and HOMA-IR



In the present study, comparison of BMI with Serum Uric Acid levelsand HOMA-IR is shown in table 25.

Table 26: Correlation between Serum uric acid and HbA1C levels by Karl Pearson's correlation coefficient method

Parameters	Correlation between Serum uric acid with		
	r-value	t-value	p-value
HbA1c	-0.0015	-0.0066	0.9948

In the present study, there is a negative correlation between SUA and HbA1c ($r = -0.0015$, $p = 0.9948$).

Table 27: Correlation between HOMA-IR with all parameters by Karl Pearson's correlation coefficient method

Parameters	Correlation between HOMA-IR with		
	r-value	t-value	p-value
Age in yrs	0.1560	1.3403	0.1844
BMI	0.4948	4.8644	0.0001*
FBS	0.2152	1.8702	0.0655
HbA1c	-0.2354	-2.0556	0.0435*
Serum uric acid	0.2283	2.0033	0.0489*
Fasting c-peptide	0.8174	12.0397	0.0001*
Creatinine	0.1989	1.7220	0.0894

*$p<0.05$

On correlating HOMA-IR with multiple variables as shown in table 19, a significant correlation was observed with BMI (p=0.0001), HbA1C (p=0.0435), SUA levels (p=0.0489) and Fasting C-Peptide values (p=0.0001)at 5% level, but not with age (p=0.1844) and serum creatinine (p=0.0894).

Table 28: Multiple linear regression analysis of HOMA-IR scores by other variables

Independent variable	Estimate	SE of estimate	t-value	p-level
Intercept	-4.6605	1.7599	-2.6481	0.0101*
Age in yrs	0.0120	0.0134	0.9003	0.3712
BMI	-0.0554	0.0642	-0.8625	0.3915
FBS	0.0216	0.0033	6.5578	0.0001*
HbA1c	-0.0425	0.0690	-0.6159	0.5401
Serum uric acid	0.1644	0.1223	1.3443	0.1835
Fasting c-peptide/ insulin	1.2364	0.0864	14.3031	0.0001*
Creatinine	-0.2674	0.8258	-0.3238	0.7471
$R=0.9151$, $R^2=0.8374$, $F(7,66)=48.590$ $p<0.05$, S Std.Error of estimate: 1.4252				

*$p<0.05$

In this study, multiple linear regression analysis of HOMA-IR (pancreatic β cell function) by other variables is shown in table 20. The coefficient of determination (R^2) is 0.8374 ($p<0.05$), indicating significant contribution of all variables when combined towards HOMA-IR.

DISCUSSION

One of the important components in pathogenesis of T2DM is the reduction in the mass of β pancreatic cells along with increasing IR. This is compensated with increased insulin secretion in the initial phases of DM. Theoretically, this elevated insulin secretion might possibly compensate for IR to maintain normoglycemia for as long as 10 years prior to the onset of overt DM. [68,69]

Past studies have proved that increasing SUA is potential risk factor for development of various cardiovascular as well as renal disorders. [70] Of late, the causal role of SUA in incident T2DM is being studied. The oxidative stress and inflammation of adipocytes caused by UA by multiple pathways contributes to IR, leading to development of T2DM. [71]

In the present hospital based cross-sectional study in newly diagnosed T2DM patients, a male preponderance was noted. 72.4% of the study population was male, and 27.6 % female, with male to female ratio of 2.62: 1. This sex distribution pattern of the study was consistent with a single centre, retrospective, observational study by ShayeKivity et al. to study the association between serum uric acid and incident type 2 diabetes mellitus on the basis of gender distribution, where 72 % of the study population was male and 28 % female. [72]

In this present study, the age of the study population ranged between 20 to 84 years. Most of the patients were more than 60 years of age (32.89%), whereas the mean age was 53.76 ± 13.33 years. Yimeng Hu et al. in their single centre, cross-sectional, observational study reported mean age of 50.21 ± 13.34 years (range - 20–85 years). [73]

In the present study, prevalence of hypertension among the study population was 48.7 %, which was consistent with a study by Wei Tang et al. which was a single centre cross-sectional observational study, where prevalence of hypertension in their study population was 48.48%. [74]

In the present study, the most common habit was tobacco consumption (55.3% of the patients), which was more common among males (63.64 %), compared to females (33.33%). The habit of alcohol consumption was observed in 11.8 % of the total study population, where as 5.3 % patients had a habit of both tobacco and alcohol consumption. These findings were comparable with a single center cross-sectional study by Yimeng Hu et al. , where tobacco consumption was a more common habit compared to alcohol consumption (28.8% vs 18.6%), and the male population had a higher prevalence of tobacco consumption (42.5%).

In this study, family history of DM was present in 46.1 % of the study population, which was in concordance with the study done by Stephen P Juraschek et al., which aimed at determining the temporal relationship amongst SUA and incident diabetes, in which 37.4 % of the newly diagnosed diabetics had family history of DM. [75]

In the present study, majority of the study population was obese (75 %), i.e. BMI ≥25 kg/m^2 and the mean BMI was 27.19 ± 3.23 kg/m^2. Among the male patients, mean BMI was 26.97 ± 3.27 kg/m^2, whereas among the female patients, it was 27.79 ± 3.13 kg/m^2 .The maximum BMI was seen in the age group of ≥61years, with a mean BMI of 28.75 ± 2.76 kg/m^2. On rest of the physical examination, 48.7 % of the patients had signs of insulin resistance. ShayeKivity et al. observed that among the incident DM cases, the mean BMI among the male population was 28.7 ± 3.6 kg/m^2 whereas among the female population, it was 27.9 ± 4.3 $kg/m^{2.}$

On studying clinical characteristics of the present study, the mean SUA levels among the male study population was 4.65 ± 1.81 mg/dl and among the females, it was 4.31 ± 1.94 mg/dl. This was similar to a study done by Yimeng Hu et al., where the SUA concentration among the male patients was 5.57mg/dl and 4.5 mg/dl among the females.

Similarly the mean HbA1c was 9.88 ± 2.67 % among males and 9.17 ± 2.98 % among females. In the study done by Wei Tang et al, similar values were noted, i.e. 9.18 ± 2.45 % in females and 9.49 ±2.47% in males.

The mean serum creatinine value in this study was 0.86 ± 0.20 mg/dl among the male patients and 0.74 ± 0.32 mg/dl among the female patients. This was in concordance with the study done by Yimeng Hu et al., in which the mean serum creatinine was 0.79mg/dl among males and 0.61mg/dl among females.

The β pancreatic cell function in the present study was estimated using HOMA-IR , which was calculated using FBS and either fasting C-peptide levels or fasting serum insulin levels using the HOMA2 calculator. The mean HOMA-IR level among the male study population was 5.01 ± 7.44 and 5.02 ± 4.63 among the female study population. In a similar study done by Yimeng Hu et al., the average HOMA-IR levels were 3.36 and 3.31 in males and females respectively, and Stephen P Juraschek et al. in their study reported an average HOMA-IR value of 4.4 ± 3.0.

In the present study, a positive and significant correlation was observed between SUA & HOMA-IR (r=0.2283, p=0.0489) at 5% level, when SUA was modelled as a continuous variable. Similar results were noted in the study done by

Stephen P Juraschek et al., where SUA when modelled as continuous variable remained significantly associated with HOMA-IR (p=0.03).

On further gender-wise stratification, in the female population SUA and HOMA –IR had a positive and significant correlation (r=0.5127, p=0.0175) at 5% level, where as in the male population the correlation was positive, but not significant (r=0.0549, p=0.6933) at 5% level. These findings were in concordance with the study done by Yimeng Hu et al., in which the female population had a positive and significant correlation between SUA and HOMA-IR (r=0.22, p<0.01), whereas in the male population, the correlation was not significant (r=0.09, p=0.14) at 5% level.

Furthermore, correlation between HOMA-IR & BMI was found to be positive & significant (r=0.4948, p=0.0001), which was also observed in the study by Yimeng Hu et al. (p<0.05). This finding supports the fact that weight loss can reduce insulin resistance.

A positive correlation was also noted between SUA & BMI (r=0.1943, p=0.0925) which was in agreement with the aforementioned study.

When the relationship between SUA and HbA1C was studied, it was observed that there was a negative correlation between the two variables (r = -0.0015, p = 0.9948). A study done by NikiKatsiki et al. showed that when HbA1C was ≥ 7%, as the HbA1C value increased, SUA levels decreased. [76]

On correlating HOMA-IR with multiple variables, a significant correlation was observed with BMI (p=0.0001), HbA1C (p=0.0435), SUA levels (p=0.0489) and Fasting C-Peptide values (p=0.0001), but not with age (p=0.1844) and serum creatinine (p=0.0894).

Using these variables, when multiple regression analysis was carried out (to identify confounding factors influencing β cell functions), coefficient of determination (R^2) was 0.8374 ($p<0.05$), indicating significant contribution of all variables when combined towards HOMA-IR, which was consistent with the study done by Yimeng Hu et al.

CONCLUSION

The present study demonstrated that serum uric acid harbours a positive and significant association with pancreatic islet β cell function index among patients of T2DM who are newly diagnosed.

SUMMARY

The present study of 76 patients titled "**ASSOCIATION BETWEEN ELEVATED SERUM URIC ACID LEVELS AND ISLET BETA CELL FUNCTION INDICES IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS**" which is a one year hospital based cross sectional study was done in the Department of Medicine, KLE'S Dr Prabhakar Kore Hospital and Medical Research Center, Belagavi from January 2019 to December 2019. The study was designed to find correlation between serum uric acid levels and pancreatic islet β cell function index (calculated using HOMA-IR) in cases of newly diagnosed type 2 Diabetes Mellitus.

The salient findings of the study are summarized as follows –

- There was a male preponderance with 72.4% of the study population being males, and 27.6 % female, with male to female ratio of 2.62 : 1.
- Majority of the patients were more than 60 years of age (32.89%), and the mean age was 53.76 ± 13.33 years.
- The prevalence of hypertension among the study population was 48.7 %.
- The most common habit among the study population was tobacco consumption (55.3%). Family history of DM was observed in 46.1 % of the patients.
- Most of the patients were obese (75 %), i.e. BMI ≥25 kg/m^2 and the mean BMI was 27.19 ± 3.23 kg/m^2.
- The mean SUA levels among the male study population were 4.65 ± 1.81 mg/dl and among the females, it was 4.31 ± 1.94 mg/dl.

- The β pancreatic cell function index was estimated using HOMA-IR. The mean HOMA-IR level among the male study population was 5.01 ± 7.44 & 5.02 ± 4.63 among the female study population.
- A positive and significant correlation was observed between SUA & HOMA-IR (r=0.2283, p=0.0489) at 5% level, & the correlation was more pronounced among the female population (r=0.5127, p=0.0175).
- Correlation between HOMA-IR & BMI was found to be positive & significant (r=0.4948, p=0.0001).
- A negative correlation was noted between SUA & HbA1C (r = -0.0015, p = 0.9948).
- On plotting multiple regression analysis, coefficient of determination (R^2) was 0.8374 ($p<0.05$), indicating significant contribution of all variables when combined towards HOMA-IR.

In newly diagnosed T2DM cases, SUA harbours a positive & significant correlation with pancreatic islet β cell index, which is influenced by gender & BMI.

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ANNEXURE I

CONSENT STATEMENT

Title: "ASSOCIATION BETWEEN ELEVATED SERUM URIC ACID LEVELS AND ISLET BETA CELL FUNCTION INDICES IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS- A ONE YEAR CROSS SECTIONAL STUDY AT KLE'S DR PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTER"

Study investigator: REG NO. BG0118005
P.G- M.D. GENERAL MEDICINE.
J.N. Medical College,
KAHER, Belagavi-10.

Co-investigator: Dr _____
Professor,
Department of Medicine
J.N. Medical College,
KAHER, Belagavi-10.

INTRODUCTION: You are being invited to participate in this study on the association between elevated serum uric acid levels and islet beta cell function indices in newly diagnosed type 2 diabetes mellitus.

EXPLANATION OF PROCEDURE: In this study we aim to find the association between elevated serum uric acid levels and islet beta cell function indices in newly diagnosed type 2 diabetes mellitus in 76 patients recently diagnosed with type 2 diabetes mellitus, admitted to K.L.E.S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

POSSIBLE BENEFITS: The investigator does not promise or guarantee that you will receive any benefit being in the study; however, it will be aimed at better understanding of the association between elevated serum uric acid levels and Islet beta cell function indices in newly diagnosed type 2 diabetes mellitus.

CONFIDENTIALITY: All information collected during the course of study will be kept confidential.

WITHDRAWAL: Participation in this study is voluntary. If you don't wish to participate in this study; you will not lose benefits to which you are entitled. After starting the study, anytime during the study, if you feel to withdraw from the study, you are free to do so.

COST OF PARTICIPATION: The cost of the study will be borne by the researcher. There will be no additional cost to you for participation 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,

DR. REG NO. BG0118005
DEPARTMENT OF GENERAL MEDICINE.
JAWAHARLAL NEHRU MEDICAL
COLLEGE,
KAHER,
BELAGAVI 590010

DR _____
PROFESSOR,
DEPARTMENT OF MEDICINE
JAWAHARLAL NEHRU MEDICAL
COLLEGE,
KAHER,
BELAGAVI 590010

Consent Statement

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, or it has been read to me, this entire consent form, and have had all my questions answered.

Participant Name: _____ Signature / Thumb print:

Investigator Name: _____ Signature:

Date:

Place:

ANNEXURE II - PROFORMA

PROFORMA / QUESTIONNAIRE TO BE USED FOR DATA COLLECTION

The proposed Proforma / questionnaire to be used for data collection for the study titled **ASSOCIATION BETWEEN ELEVATED SERUM URIC ACID LEVELS AND ISLET BETA CELL FUNCTION INDICES IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS – A ONE YEAR CROSS SECTIONAL STUDY AT KLE'S DR PRABHAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE**

Is as follows –

A) PATIENT IDENTIFICATION DATA -

1. Name: _____
2. IP No: _____
3. Age: _____
4. Sex: _____
5. D.O.A.: _____
6. Address: _____
7. Religion: _____
8. Marital Status: _____
9. Occupation: _____

B) PRESENTING COMPLAINTS -

C) PAST HISTORY -

D) PERSONAL HISTORY -

E) FAMILY HISTORY -

F) GENERAL PHYSICAL EXAMINATION -

1. **Anthropometric measurements –**
    - Height -
    - Weight -
    - BMI -

2. **Vitals –**
    - PR -
    - BP -
    - RR -
    - Temperature -

3. **Skin examination** (markers of insulin resistance) –

4. **Fundoscopy –**

G) SYSTEMIC EXAMINATION -

1. **CVS –**

2. **RS –**

3. **PER ABDOMEN –**

4. **CNS –**

H) INVESTIGATIONS -

1. FBS	
2. PPBS	
3. HbA1C	
4. Serum Uric acid	
5. Fasting C-peptide	
or Fasting Serum Insulin	
6. Serum Creatinine	
7. EGFR	
8. HOMA-IR	

ANNEXURE III.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
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/55 **Date: 24/11/2018**

To,

REG NO. BG0118005
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 **"ASSOCIATION BETWEEN ELEVATED SERUM URIC ACID LEVELS AND ISLET BETA CELL FUNCTION INDICES IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS – A ONE YEAR CROSS SECTIONAL STUDY AT KLE'S DR PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE ",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
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.

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ANNEXURE IV - KEY TO MASTERCHART

S. No. - Serial Number

IP No. - Inpatient Number

OP No. - Outpatient Number

FBS - Fasting Blood Sugar

HOMA-IR -Homeostatic Model Assessment for Insulin Resistance

BMI - Body Mass Index

IR Signs - Insulin Resistance signs

HbA1C -Glycosylated Haemoglobin

In. - Fasting Serum Insulin

S.No.	IP No	OP No	AGE	SEX	FBS	HBA1C	SERUM URIC ACID	FASTING C-PEPTIDE/ INSULIN	HOMA - IR	CREATININE	BMI	IR SIGNS	HABIT	FAMILY HISTORY	HYPERTENSION
1	978843	5466753	67	M	223	11.3	3.6	2.14	2.14	0.84	25	ABSENT	ALCOHOL	ABSENT	ABSENT
2	978949	5466986	35	M	202	6.9	2.6	1.41	1.35	0.92	26.8	ABSENT	ALCOHOL	MOTHER	ABSENT
3	978311	610408	59	M	167	10.1	4.1	2.81	2.5	0.91	30	PRESENT	ALCOHOL	ABSENT	ABSENT
4	978688	5465321	59	M	260	10.8	4.4	0.89	1	1.15	29	ABSENT	TOBACCO	ABSENT	PRESENT
5	978351	5463365	63	F	177	10.4	2.7	4.57	4.13	0.52	30	PRESENT	ABSENT	ABSENT	PRESENT
6	977733	5458538	34	M	203	6.5	4.9	2.64	2.52	0.93	27	ABSENT	TOBACCO	MOTHER	ABSENT
7	976915	5454272	60	F	140	7.3	2	1.8	1.52	0.79	22	ABSENT	ABSENT	MOTHER	ABSENT
8	977688	5458488	64	M	178	7.1	5.2	5.75	5.21	0.75	32	PRESENT	TOBACCO	ABSENT	PRESENT
9	977412	5457000	70	F	195	7.2	4.2	6.9	6.41	1.4	32	PRESENT	ABSENT	MOTHER	PRESENT
10	977197	5455291	65	F	195	7.9	3.8	5.11	4.78	0.49	31	PRESENT	ABSENT	ABSENT	PRESENT
11	974779	5441301	55	M	176	8.4	3.8	8.05	7.25	0.74	33	PRESENT	TOBACCO	FATHER	ABSENT
12	974790	5441312	36	M	290	6.5	6.6	3.82	4.95	0.91	34	PRESENT	TOBACCO	FATHER	ABSENT
13	973093	5432110	71	F	147	6.7	2.3	8.58	7.25	0.52	33.5	PRESENT	TOBACCO	ABSENT	PRESENT
14	974055	5437747	48	M	199	8.7	1.6	3.94	3.72	1.09	28	ABSENT	TOBACCO	ABSENT	ABSENT
15	974223	5438564	61	M	268	7.8	5.5	2.85	3.31	0.68	29	PRESENT	TOBACCO, ALCOHOL	MOTHER	PRESENT
16	971484	915716	65	F	171	6.6	1.8	2.01	1.81	0.51	22	ABSENT	ABSENT	ABSENT	ABSENT
17	972946	5430799	58	F	156	7	3.2	4.61	4	0.74	29	PRESENT	ABSENT	MOTHER	PRESENT
18	968261	5401047	73	M	355	8.5	9.7	2.91	6.02	1.3	31	PRESENT	TOBACCO	ABSENT	PRESENT
19	968890	5404106	41	F	194	10.6	4.3	5.28	4.93	0.7	27	PRESENT	TOBACCO	ABSENT	PRESENT
20	969042	5238379	49	M	181	14	4.2	4.02	3.68	0.67	26	PRESENT	TOBACCO	ABSENT	ABSENT
21	952644	5295211	38	M	376	7.6	11.3	0.77	2.01	1.2	24	ABSENT	ABSENT	ABSENT	ABSENT
22	946143	5253824	68	F	217	10	8.2	3.63	3.56	1.26	28	PRESENT	ABSENT	FATHER	PRESENT
23	968986	5405313	42	M	286	10.7	6.5	4.12	5.21	1	33	PRESENT	TOBACCO	ABSENT	PRESENT
24	961609	5356171	51	M	352	13.5	3.2	1.23	2.49	0.83	23	ABSENT	TOBACCO	ABSENT	PRESENT
25	960899	4704380	80	M	322	7.7	6.9	In. - 25.2	5.81	0.91	27	ABSENT	TOBACCO	SISTER	PRESENT
26	953212	2795027	50	M	259	11.3	3.6	2.2	2.46	0.67	23	ABSENT	ABSENT	MOTHER	ABSENT
27	948772	5157528	49	M	162	6.7	7.1	2.24	1.98	0.68	21	ABSENT	TOBACCO	FATHER	ABSENT
28	974583	4603178	53	M	263	11.3	6.7	7.69	8.62	1.09	34	PRESENT	ABSENT	ABSENT	PRESENT
29	974350	4548619	47	M	173	11.1	3.1	1.93	1	0.74	22	ABSENT	ABSENT	FATHER	ABSENT
30	978911	5466947	62	M	212	11.4	5.3	8.04	7.75	1.1	32	PRESENT	TOBACCO	MOTHER	PRESENT
31	958958	5336226	56	M	303	10.3	3	1.78	2.5	0.73	22	ABSENT	TOBACCO, ALCOHOL	ABSENT	ABSENT
32	951164	5286278	58	M	253	6.5	4.2	1.85	2.02	1.11	21	ABSENT	TOBACCO	ABSENT	PRESENT
33	961713	5071468	46	F	303	13.1	6.5	1.8	2.53	0.63	27.3	ABSENT	ABSENT	ABSENT	ABSENT
34	966898	5391652	22	F	206	14.7	3.6	0.9	0.87	0.53	25.3	PRESENT	ABSENT	MOTHER	ABSENT
35	978693	4387980	84	F	160	9.4	5.1	2.56	2.25	0.89	28	ABSENT	ABSENT	ABSENT	PRESENT
36	979639	5470023	46	M	238	10.4	3.3	0.92	0.96	0.72	27.8	ABSENT	ALCOHOL	ABSENT	ABSENT
37	980243	5475870	52	F	286	11.9	4	5.36	6.76	0.62	30.1	PRESENT	TOBACCO	ABSENT	PRESENT
38	979926	5468593	47	M	383	12.6	5.9	2.22	6.25	1.06	26.9	ABSENT	ABSENT	ABSENT	ABSENT
39	980023	5474509	40	M	248	14.7	3.5	1.55	1.67	0.65	25.1	ABSENT	TOBACCO	ABSENT	ABSENT
40	978469	5463744	20	F	202	6.5	5.4	8.41	7.94	0.83	27.4	PRESENT	ABSENT	MOTHER	ABSENT
41	983668	5495429	69	F	273	7.3	4.6	6.09	7.19	0.67	29.6	ABSENT	TOBACCO	FATHER	PRESENT
42	982947	5491037	72	F	271	17.6	2.4	1.23	1.46	0.46	28.3	ABSENT	TOBACCO	FATHER	PRESENT

S.No.	IP No	OP No	AGE	SEX	FBS	HBA1C	SERUM URIC ACID	FASTING C-PEPTIDE/ INSULIN	HOMA - IR	CREATININE	BMI	IR SIGNS	HABIT	FAMILY HISTORY	HYPERTENSION
46	982691	5478629	55	F	324	7.7	2.5	4.53	7.25	0.63	25.5	ABSENT	TOBACCO	FATHER	ABSENT
47	982882	5490367	57	M	165	6.5	3.7	5.05	4.46	1.15	27	PRESENT	TOBACCO	MOTHER	ABSENT
48	981525	2058514	52	M	150	8.9	2.8	13	14.25	1.01	26.4	PRESENT	TOBACCO	MOTHER	PRESENT
49	982562	5488849	45	M	148	8.9	5.7	3.04	2.6	0.74	26.2	ABSENT	TOBACCO, ALCOHOL	MOTHER	ABSENT
50	981959	5485378	57	M	282	17	4.9	0.8	1	0.79	24.7	ABSENT	TOBACCO	ABSENT	PRESENT
51	982341	5487221	68	F	387	8.4	9.2	7.9	22.73	1.02	31.6	PRESENT	TOBACCO	ABSENT	PRESENT
52	981599	5482708	73	M	189	8.5	4.1	3.4	3.15	1.02	28.4	ABSENT	ALCOHOL	ABSENT	PRESENT
53	981186	5235123	61	M	250	10.2	2.3	5.34	5.75	0.56	28.7	PRESENT	TOBACCO	ABSENT	PRESENT
54	981615	5482717	61	M	188	9.2	3.6	6.99	6.41	0.81	28.4	ABSENT	ALCOHOL	MOTHER	ABSENT
55	981369	5480962	75	M	267	7	6.3	5.24	6.02	0.86	29.4	PRESENT	TOBACCO	ABSENT	ABSENT
56	983723	5495943	41	M	298	8.7	3.5	9.82	12.99	0.85	30.4	PRESENT	TOBACCO	ABSENT	PRESENT
57	982135	5485855	45	M	222	13.3	2.3	3.39	3.37	0.82	28.1	ABSENT	ALCOHOL	ABSENT	ABSENT
58	983389	754385	66	M	152	8.4	3.6	3.47	2.99	0.74	24.7	PRESENT	TOBACCO	FATHER	PRESENT
59	984090	3084613	57	M	155	6.8	6.3	6.29	5.43	0.93	25.6	ABSENT	ALCOHOL	ABSENT	PRESENT
60	980217	5475625	63	M	452	9.7	8.1	1.23	55.56	1.2	26.9	PRESENT	TOBACCO	MOTHER	ABSENT
61	989104	3562524	64	M	267	12.8	3.9	2.66	3.08	0.76	24.7	ABSENT	TOBACCO	ABSENT	PRESENT
62	989422	5341038	65	M	283	10.2	6.5	3.63	4.52	1.1	30.6	PRESENT	TOBACCO	ABSENT	PRESENT
63	988727	5529294	56	M	119	10.4	4.5	7.09	5.65	0.69	28.1	PRESENT	TOBACCO	ABSENT	ABSENT
64	988888	5530198	44	M	190	8	5.4	0.33	1.91	1.18	24.8	ABSENT	ABSENT	ABSENT	ABSENT
65	987123	5516576	47	F	207	7.9	4	2.77	2.67	0.57	25.8	PRESENT	ABSENT	FATHER	ABSENT
66	987300	5481549	34	F	211	7.3	5	3.01	2.92	0.6	23.2	ABSENT	ABSENT	MOTHER	ABSENT
67	986065	5510429	55	M	249	15.6	3.6	1.25	1.35	0.57	21.5	ABSENT	ALCOHOL	ABSENT	PRESENT
68	986103	4776742	61	F	249	7.1	5.7	2.32	2.5	0.6	26.9	PRESENT	ABSENT	ABSENT	PRESENT
69	991720	5551460	45	M	235	6.7	3.6	6.12	6.25	0.66	28.1	PRESENT	TOBACCO	FATHER	ABSENT
70	990299	5540921	60	M	208	8.9	4.3	6.04	5.78	1.03	23.2	ABSENT	TOBACCO	MOTHER	ABSENT
71	989848	3200918	48	M	261	9.2	4.7	2.91	3.28	0.75	24	ABSENT	TOBACCO	MOTHER	PRESENT
72	991819	5552081	57	M	206	7.8	5.4	2.76	2.65	0.76	28	PRESENT	TOBACCO	ABSENT	PRESENT
73	992062	5551178	21	M	260	16.6	2.9	1.95	2.19	0.5	26.2	ABSENT	ABSENT	MOTHER	ABSENT
74	992513	3705443	55	M	165	7.6	4	3.61	3.19	0.87	23	ABSENT	TOBACCO	MOTHER	ABSENT
75	972960	5430767	38	M	180	12.4	5	5.11	4.65	1	27.1	PRESENT	TOBACCO	MOTHER	ABSENT
76	990543	5389530	50	M	165	8.9	3.4	5.45	4.81	0.7	28.7	PRESENT	TOBACCO	MOTHER	PRESENT