“ROLE OF XANTHINE OXIDASE AND URIC ACID IN METABOLIC SYNDROME”

By

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IN

GENERAL MEDICINE

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ABSTRACT

BACKGROUND: Patients with metabolic syndrome are at a high risk of developing diabetes and CVD; therefore, early intervention, primarily lifestyle modifications, can ultimately prevent these costly and deadly diseases.

AIMS: To determine the role of xanthine oxidase and uric acid in metabolic syndrome.

MATERIALS & METHODS: Cross-sectional, hospital-based observational study conducted for a period of one and half year from January 2019 to July 2020 in a population of 128 participants.

RESULTS: The mean age of participants was 55.64±12.61 years. Majority of the participants in the study population were males with 61.72%. Fasting blood sugar, uric acid and serum xanthine oxidase were identified with 172.21 ± 87.42, 7.58 ± 0.74 and 2.99 ± 0.91 in participants with the metabolic syndrome. The Uric Acid was ≥7.35 for 70.31% participants with metabolic syndrome. Whereas, the Serum xanthine oxidase was ≥1.95 for 88.71% of participants. The uric acid had sensitivity, specificity, false positive rate, false-negative rate, positive predictive value, negative predictive value and total diagnostic accuracy of 70.31%, 76.56%, 23.44%, 29.69%, 75%, 72.06% and 73.44% in predicting the presence of the metabolic syndrome. The serum xanthine oxidase had sensitivity, specificity, false positive rate, false-negative rate, positive predictive value, negative predictive value and total diagnostic accuracy of 88.71%, 90.63%, 9.38%, 11.29%, 90.16%, 89.23% and 89.68% in predicting the presence of the metabolic syndrome.

Conclusion: A strong association was found between uric acid, xanthine oxidase and prevalence of metabolic syndrome. This also indicated that the waist circumference, uric acid, serum xanthine oxidase and HDL levels can indicate the risk of developing metabolic syndrome.

Keywords: serum uric acid, metabolic syndrome, waist circumference, xanthine oxidase, diabetes mellitus

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LIST OF ABBREVIATIONS

GLOSSARY	ABBREVIATIONS
ATP	Adenosine triphosphate
BP	Blood pressure
CDC	Centers for disease control
CI	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CVS	Chorionic villus sampling
DM	Diabetes mellitus
FBS	Fasting blood sugar
FDA	Food and drug administration
HDL	High-density lipoprotein
HOMA	Homeostatic model assessment
HTN	hypertension
IR	Insulin resistance
MetS	Metabolic syndrome
ROC	Receiver operative curve
ROS	Review of systems
SBP	Spontaneous bacterial peritonitis
SUA	Serum uric acid
TG	Triglycerides
WC	White cells
XDH	Xanthine dehydrogenase
XO	Xanthine oxidase
XOR	Xanthine oxidoreductase

INTRODUCTION

INTRODUCTION:

Metabolic syndrome is a multifactorial pathological condition defined by the association of several metabolic disorders.

The visceral obesity, dyslipidemia with high triglycerides or low level of high-density lipoprotein cholesterol, hypertension and fasting hyperglycemia is included in metabolic disorders. The diagnostic for metabolic syndrome is the presence of any 3 of these five alterations.[1, 2]

In south Asian countries like India prevalence of obesity and metabolic syndrome is rapidly increasing. It leads to an increased rate of mortality and morbidity.[3] The evidence of the metabolic syndrome is identified in one third of the urban South Asians.[4] In US, the estimated prevalence of metabolic syndrome in men and women were 25.2% and 29% whereas, in Europe 15.7% and 14.2% and China with 9.8% and 17.8%.[5-7]

The risk of metabolic syndrome is increased with age, female gender, general obesity, inadequate fruit intake, hypercholesterolemia, and middle-to-high socioeconomic status.[8] Insulin resistance, adipose tissue dysfunction, chronic inflammation, oxidative stress, circadian disruption, microbiota, genetic factors, and maternal programming are the major contributing factors and mechanisms involved in the metabolic syndrome.[9] The clinical presentations involved in the metabolic syndrome are hypertension, dyslipidemia, non-alcoholic fatty liver disease, polycystic ovarian syndrome, sleep and breathing disorders, Alzheimer's disease and cancers such as breast, prostate and pancreas.

Xanthine oxidoreductase can be a contributor to the pathogenesis of metabolic syndrome through the oxidative stress and the inflammatory response induced by XOR-derived reactive oxygen species and uric acid. Hyperuricemia is closely associated with hypertension, insulin resistance, obesity and hypertriglyceridemia. There is a correlation identified between the serum level of XOR, triglyceride/high-density lipoprotein cholesterol ratio, fasting glycemia, fasting insulinemia and insulin resistance index. Also, the increased activity of endothelium-linked XOR can promote hypertension.[10]

THE NEED FOR THE STUDY:

Serum uric acid and xanthine oxidase concentration was positive, with the prevalence of metabolic syndrome. Hence, more studies are required to explore the mechanisms of the relationship. Patients with metabolic syndrome, are at a greater risk of emerging diabetes and CVD; therefore, early intervention, primarily lifestyle modifications can ultimately prevent these costly and deadly diseases. The present study was directed to determine the role of xanthine oxidase and uric acid in metabolic syndrome.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES:

1. To study the role of xanthine Oxidase (XO) in metabolic syndrome (MetS).
2. To study the role of uric acid in metabolic syndrome.
3. To assess the sensitivity and specificity of Xanthine Oxidase and uric acid in the diagnosis of metabolic syndrome.

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

1. METABOLIC SYNDROME –

a) Definition

The metabolic syndrome is the co-occurrence of several known cardiovascular risk factors, including insulin resistance, atherogenic dyslipidemia, obesity and hypertension.[11] Abdominal obesity, raised blood pressure, atherogenic dyslipidemia, insulin resistance ± glucose intolerance, proinflammatory, and prothrombotic states are the ATP III identified six components of the metabolic syndrome. Hypertension, dyslipidemia, nonalcoholic fatty liver disease, polycystic ovarian syndrome, sleep and breathing disorders, Alzheimer's disease and cancers such as breast, prostate and pancreas are the multiple clinical presentations involved in the metabolic syndrome.[12]

Figure 1: Definitions of metabolic syndrome.[11]

	NCEP ATP III (2005 revision)	WHO (1998)	EGIR (1999)	IDF (2005)
Absolutely required	None	Insulin resistance* (IGT, IFG, T2D or other evidence of IR)	Hyperinsulinemia‡ (plasma insulin >75th percentile)	Central obesity (waist circumference§): ≥94 cm (M), ≥80 cm (F)
Criteria	Any three of the five criteria below	Insulin resistance or diabetes, plus two of the five criteria below	Hyperinsulinemia, plus two of the four criteria below	Obesity, plus two of the four criteria below
Obesity	Waist circumference: >40 inches (M), >35 inches (F)	Waist/hip ratio: >0.90 (M), >0.85 (F); or BMI >30 kg/m^2	Waist circumference: ≥94 cm (M), ≥80cm (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥100 mg/dl or Rx	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥100 mg/dl
Dyslipidemia	TG ≥150 mg/dl or Rx	TG ≥150 mg/dl or HDL-C: <35 mg/dl (M), <39 mg/dl (F)	TG ≥177 mg/dl or HDL-C <39 mg/dl	TG ≥150 mg/dl or Rx
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx			HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx
Hypertension	>130 mmHg systolic or >85 mmHg diastolic or Rx	≥140/90 mmHg	≥140/90 mmHg or Rx	>130 mmHg systolic or >85 mmHg diastolic or Rx
Other criteria		Microalbuminuria†		

*IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies.
†Urinary albumin excretion of ≥20 µg/min or albumin-to-creatinine ratio of ≥30 mg/g.
‡Reliable only in patients without T2D.
§Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women.
Rx, pharmacologic treatment.

b) epidemiology,

The prevalence of metabolic syndrome often parallels the occurrence of obesity and type 2 diabetes mellitus. About 30.2 million adults age 18 years or older, in essence, 12.2% of USA adults had type 2 diabetes as per CDC data published in 2017. Whereas *23.8%* were not aware of having diabetes. Metabolic syndrome was identified as in one third of US adults.[13] The prevalence of metabolic syndrome along with the incidence of abdominal obesity was higher in the South Asian Americans.[14]

In China, as per the WHO criterion, the incidence of obesity and overweight increased from 14.6 to 21.8% between the year 1992 and 2002. In urban areas, the incidence of metabolic syndrome increased from 8 to 10.6% whereas 4.9 to 5.3% in rural areas. [13] In the year 2017, the prevalence of metabolic syndrome was about 15.5%.[15] The occurrence of the metabolic syndrome in the Asian population and the European population was 12–37% and 12–26% respectively.[16]

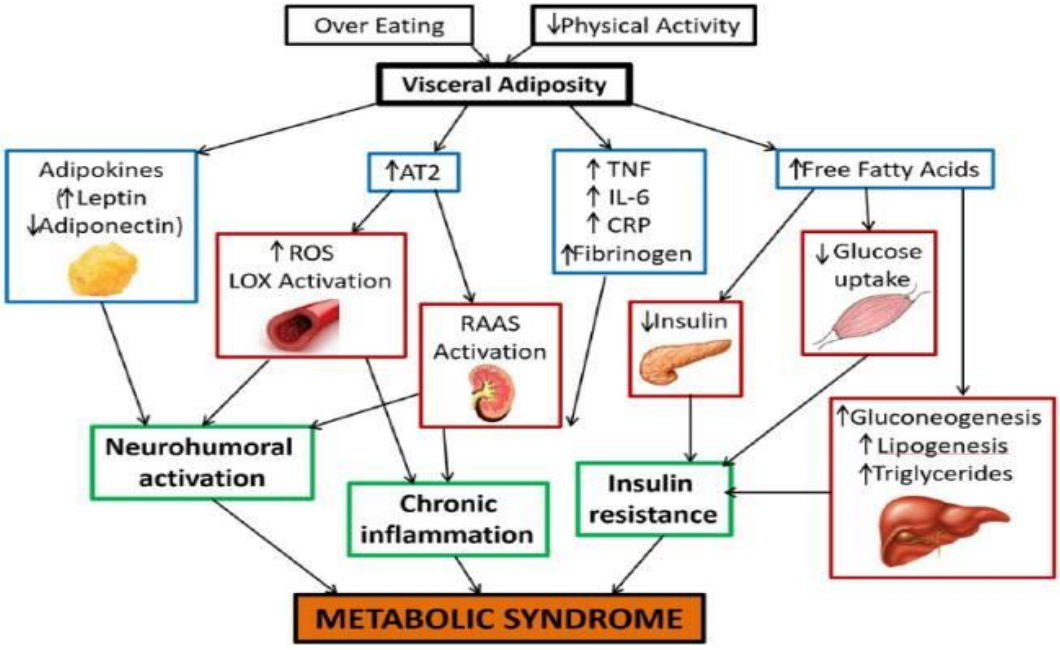
c) causes, risk factors, pathogenesis

Genetic and environmental are the underlying causes of the metabolic syndrome that includes overweight, obesity, and physical inactivity, which in turn lead to insulin resistance, hyperinsulinemia, endothelial dysfunction and inflammation. [12] Abdominal obesity, physical inactivity and atherogenic/diabetogenic diet are the underlying risk factors for the metabolic syndrome.[17]

Consumption of excess calories and lack of physical activity is the major contributor to the metabolic syndrome. The primary trigger for most of the pathways involved in MetS is the visceral adiposity. The major mechanisms involved in the initiation, progression and

transition of MetS to CVD are the insulin resistance, neurohormonal activation and chronic inflammation.[18]

Figure 2: Pathophysiological mechanisms in the metabolic syndrome.[19]



d) Diagnosis

Table 1: API III clinical identification of the metabolic syndrome.[20]

Risk factors	Defining levels
Abdominal obesity, given as waist circumference.	
Men	≥ 102 cm (≥ 40 in)
Women	≥ 88cm (≥ 35 in)
Triglycerides	≥ 150 mg/dl
HDL cholesterol	
Men	< 40 mg/dl
Women	< 50 mg/dl
Blood pressure	≥ 130/≥85mm Hg
Fasting glucose	≥ 110mg/dl

e) Treatment

Table 2: Therapeutic goals and recommendations for managing metabolic syndrome.[21]

Therapeutic target & goals of therapy	Therapeutic Recommendations
Lifestyle risk factors	Long-term prevention of CVD and prevention (or treatment) of type 2 DM
Obesity of the abdomen	
Reduce body weight by 7% to 10% during the first year of therapy. Continue weight loss after that to the extent possible with a goal to ultimately achieve desirable weight (BMI <25 kg//m2)	A gradual slow weight reduction at the rate of 7% to 10% from the baseline is recommended with balanced physical activity and caloric intake.
Physical inactivity	
Regular moderate-intensity physical activity; at least 30 min of continuous or intermittent (and preferably ≥60 min) 5 d/week, but preferably daily	In patients with established CVD, assess risk with detailed physical activity history and/or an exercise test, to guide prescription. Encourage 30 to 60 min of moderate-intensity aerobic activity: brisk walking, preferably daily, supplemented by an increase in daily lifestyle activities (eg, pedometer step tracking, walking breaks at work, gardening, housework). Longer exercise times can be achieved by accumulating exercise throughout the day. Encourage resistance training 2 d/wk. Advise medically supervised programs for high-risk patients (e.g., recent acute coronary syndrome or revascularization, CHF).
Atherogenic diet	
Reduced intake of saturated fat, trans fat, cholesterol	Recommendations: saturated fat <7% of total calories; reduce trans fat; dietary cholesterol <200 mg/dL; total fat 25% to 35% of total calories. Most dietary fat should be unsaturated; simple sugars should be limited.
Metabolic risk factors	Shorter-term prevention of CVD or treatment of type 2 DM
Elevated BP	
Reduce BP to at least achieve BP of <140/90 mm Hg (or <130/80 mm Hg if diabetes present). Reduce BP further to the extent possible through lifestyle changes.	For BP ≥140/90 mm Hg (or ≥130/80 mm Hg for individuals with chronic kidney disease or diabetes): As tolerated, add BP medication as needed to achieve goal BP For BP ≥120/80 mm Hg: Initiate or maintain a lifestyle modification in all patients with metabolic syndrome: weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products
Elevated glucose	
For IFG, delay progression to type 2 diabetes mellitus. For diabetes, HbA_1C<7.0%	For type 2 diabetes mellitus, lifestyle therapy, and pharmacotherapy, if necessary, should be used to achieve near-normal HbA1C (For IFG, encourage weight reduction and increased physical activity. <7%). Modify other risk factors and behaviours (e.g., abdominal obesity, physical inactivity, elevated BP, lipid abnormalities).

2. ROLE OF XANTHINE OXIDASE IN METABOLIC SYNDROME

What is xanthine oxidase and XOR?

Xanthine oxidase is an enzyme that is required for uric acid production by the breakdown of purine nucleotides.[22] Whereas, xanthine oxidoreductase, is an enzyme that converts the hypoxanthine to xanthine and the latter to uric acid. These are the last 2 steps of purine catabolism in the highest uricotelic primates.[23] Xanthine oxidoreductase is involved in the pathogenesis of metabolic syndrome through oxidative stress and inflammatory response. It is induced by the XOR-derived reactive oxygen species and uric acid. Triglyceride/high-density lipoprotein cholesterol ratio, fasting insulinemia, fasting glycemia and insulin resistance index are sturdily linked with the serum level of XOR.[23]

XOR released from the dead cells enter into the circulation and adhere to the endothelial binding sites of heparin, ROS, RNA and uric acid produced by the endothelial linked XOR. It contributes to the physiological modulation of arteriolar tone. Also responsible for the endothelial dysfunction.

Role in the human body:

Catabolism of purine nucleic acids is the primarily function of xanthine oxidase. The purines, guanine monophosphate and adenosine monophosphate are converted into either hypoxanthine or xanthine through a series of reactions. Xanthine oxidase catalyzes the breakdown of hypoxanthine and xanthine into uric acid. Uricase is an enzyme that converts the uric acid into allantoin, a water-soluble molecule excreted in the urine. [22]

Xanthine oxidase is vital as the cell turnover is a constant process throughout the body, and endogenous or ingested purines are continually being degraded and renewed. The reaction

that is carried out by xanthine oxidase reduces the supply of oxygen into the superoxide anion that can, in due course, progresses into hydrogen peroxide. The excess amount of hydrogen peroxide in the body is considered toxic to the cells. It is also involved in aging and a multitude of conditions such as diabetes and neurodegenerative disorders such as Alzheimer disease.[23]

Uric acid is also known to be harmful. The urate behaves as a pro-oxidant that induces the formation of other radicals. It has the ability to oxidize the lipid membranes, thereby explains the connotation between obesity and hyperuricemia. Damaging of cellular structures and DNA and proteins were caused by the Reactive oxygen species. The oxidative stress caused by the uric acid is associated with the development of hypertension, diabetes, kidney disease and cardiovascular diseases. [22]

XOR catalytic activities:

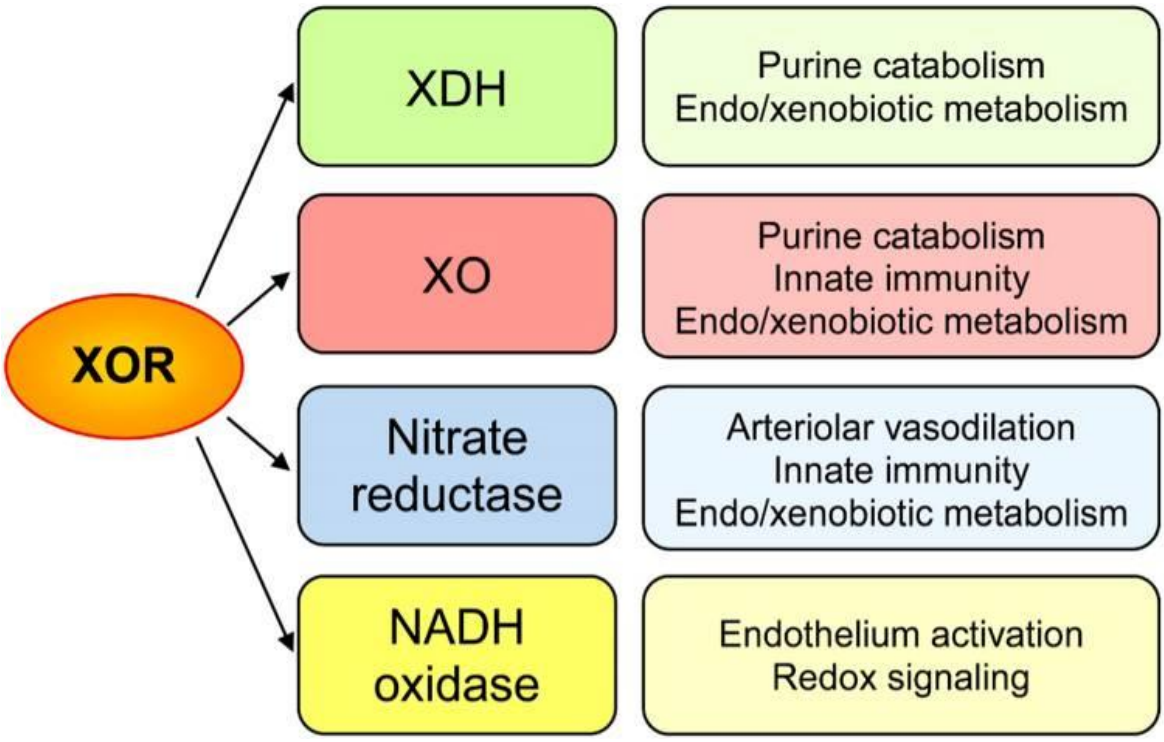
XO is the form prevailing in biological fluids, such as milk and plasma. [6]The transition from XDH to XO includes an intermediate XOR form with both the NAD+- dependent dehydrogenase and the O2-dependent oxidase activities

Xanthine oxidoreductase belongs to the metalloflavoenzymes family. It is derived from the XOR coding gene system. The enzyme has only dehydrogenase activity in the lower organism whereas, it has 2 interchangeable activities (xanthine hydrogenase and xanthine oxidase) in the mammals. XDH is the native form of xanthine oxidoreductase that is usually present inside the cells. Either by oxidation of sulfhydryl groups or limited proteolysis, the XDH gets converted into XO.

An intermediate XOA form with NAD+ dependent dehydrogenase and O_2 dependent oxidase activities are involved in the transition of XDH to XO. Transition metals and reactive oxygen species produced by XOR are able to generate highly cytotoxic hydroxyl radical through the Haber Weiss and Fenton reactions. Thus the oxidant species produced by XOR can influence the redox equilibrium and can also implicate in many biological processes.

In uricotelic parameters, XOR catalyses the last two steps of purine catabolism. In the condition of low PH and hypoxia, XOR can have NADH and nitrate reductase activities. Thereby, generates the superoxide anions and nitrous oxide. The endogenous and xenobiotic compound such as drugs can be metabolized by the broad substrate specificity and different catalytic activities of XOR.

Figure 3: XOR catalytic activities.[24]



The molecular structure of XOR proteins is homodimeric and each monomer has 3 domains. The C-terminal domains have a molybdenum-containing molybdopterin cofactor whereas, the intermediate one has a flavin adenine dinucleotide cofactor and the N terminal one has two unequal iron sulphur redox clusters. The electrons are transferred from molybdenum-containing molybdopterin cofactor to flavin adenine dinucleotide cofactor by ferredoxin centres during the process of catalysis.

The expression of XOR can be increased by various cytokines, growth factor, hormones and low oxygen tension. The post-translational modulation can give rise to XOR demolybdo or desulfo forms. Because of the moco site blockage, they are inactive in purine oxidative hydroxylation and nitrate reductase activities. Similarly, the production of oxidant species is not lost at the FDA site.

The reactive nitrogen species are formed by the XOR activities through the generation of ROS and NO. It is essential for antibacterial activity during the phagocytosis. In various pathological conditions such an ischemia/ reperfusion infusion, the XOR derived ROS and RNS can be identified as harmful. [24]

Pathophysiology:

Hereditary xanthinuria type 1 is a condition caused due to the deficiency of xanthine oxidase. It causes a mutation in the XDH gene that results in a decreased amount of xanthine oxidase production. Systemic levels of xanthine get elevated by the decreased metabolism of xanthine.

The rare xanthine kidney stones are formed by the precipitates of xanthine in the renal tubules. It obstructs the renal parenchyma and can result in renal failure if it is untreated. The excess build up of xanthine from protein breakdown can be prevented by limiting the intake of proteins. It also prevents the worsening of disease into a more severe state. The final protein product fails to incorporate a sulfur molecule into its core in subjects with type 2 of the condition that can limit the functionality of the protein.[22]

ROLE of XO/ XOR inhibitors in metabolic syndrome:

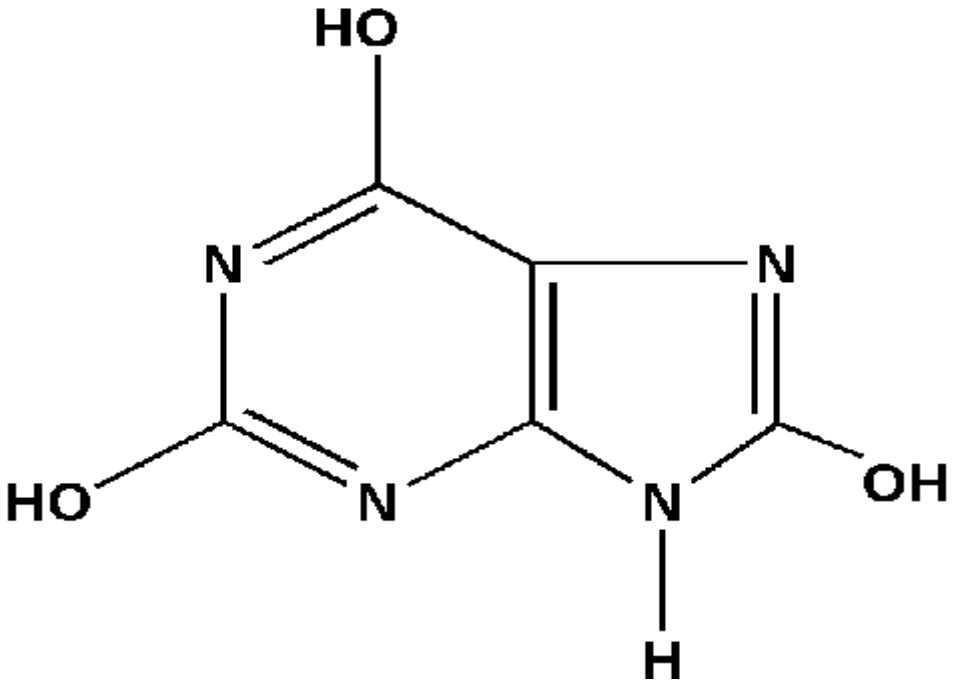
Xanthine oxidoreductase can be a contributor to the pathogenesis of metabolic syndrome through the oxidative stress and the inflammatory response induced by XOR-derived reactive oxygen species and uric acid. There is a correlation identified between the serum level of XOR, triglyceride/high-density lipoprotein cholesterol ratio, fasting insulinemia, fasting glycemia and insulin resistance index. Also, the increased activity of endothelium-linked XOR can promote hypertension.[10]

3. ASSOCIATION BETWEEN METABOLIC SYNDROME AND URIC ACID

What is uric acid, molecular structure, functions:

Uric Acid is a product of protein metabolism. It is a white crystalline, odourless and tasteless substance. It is found in blood and urine, as well as trace amounts in various organs of the body. It can accumulate and form stones or crystals in various disease states. Uric acid is an antioxidant and also has a compensatory role in response to increased oxidative stress in conditions such as cardiovascular disease. The inhibitory effect on nitric oxide production, induction of platelet aggregation and pro-inflammatory activity is the injurious impacts of uric acid.[25]

Figure 4: Molecular structure of uric acid.[26]



Role of uric acid in the metabolic syndrome:

An elevated level of uric acid is frequent in all metabolic syndrome patients. The development of metabolic syndrome, hypertension, diabetes, stroke and CVS events can be predicted with hyperuricemia.[27-29] One of the sovereign risk factor for renal dysfunction in the normal population and patients with hypertension, diabetes, and CKD is the hyperuricemia.[30-33]

Hyperuricemic patients had an odds ratio of 1.6-fold higher for emerging metabolic syndrome in the study conducted by Chen et al.[34] The study[35], conducted by Osgood and colleagues concluded the association between serum uric acid, concomitant insulin action, blood pressure, lipid profile, future IR (insulin resistance) and T2D. Uric acid production can be increased by a fructose-rich diet and can also induce the components of metabolic syndrome. Fructose-induced hyperuricemia can lead to fructose-induced insulin resistance. There is a key role for IR in the causal association among metabolic syndrome, diabetes type 2 and hyperuricemia.[25]

Babio N et al[36], conducted a cross-sectional and prospective study. This study assessed the relation between serum uric acid (SUA) concentrations and the metabolic syndrome in elderly people at high circulatory risk. Participants in the maximum baseline sex-adjusted SUA quartile was identified with an increased frequency of metabolic syndrome. The risk of developing metabolism syndrome was identified more in the population with upper quartile serum uric acid, participants initially free of hypertriglyceridemia at baseline, low high-density lipoprotein cholesterol and hypertension components of metabolic syndrome during the follow-up period. The study concluded the role of increased SUA concentration in the development of the metabolic syndrome.

BonakdaranS et al[37], performed a cross-sectional study in 1978 participants. The purpose of the study was to assess the prevalence of hyperuricemia and its connotation with metabolic syndrome in type 2 diabetes mellitus. The study results revealed that 12.7% and 65.5% were the prevalence of hyperuricemia and metabolic syndrome. The occurrence of metabolic syndrome highest and lowest quartile of uric acid levels were .7% and 65.5% respectively. The frequency of metabolic syndrome in the highest quartile of uric acid levels were 74.4% whereas, 55.9% in the lowest quartile. There was a positive correlation identified between

serum uric acid and cholesterol, triglyceride, non-HDL cholesterol, whereas a negative correlation with fasting blood sugar, glycosylated hemoglobin and HDL cholesterol. Cholesterol, triglyceride, creatinine and FBS were the independent biochemical predictors of hyperuricemia. Through the present study, it was concluded that the prevalence of MS and its components increases with increasing levels of uric acid in type 2 diabetes.

Chen D et al[38], performed a cross-sectional cohort study. The study aimed to determine the connotation between SUA and MS and its components. The study results revealed a negative correlation between SUA and high-density lipoprotein cholesterol whereas, a positive correlation with blood pressure, triglycerides, waist circumference and body mass index. The incident MS after adjusted for age, blood pressure, glucose, TG, HDL-c, smoking, alcohol drinking and education were positively correlated with the risk of developing metabolic syndrome, serum uric acid concentrations. The present study concluded that the augmented serum uric acid concentration can be a sovereign risk factor for metabolic syndrome.

Choi H et al[39], conducted a cross-sectional study in 2940 participants. The objective of the study was to assess the connotation between SUA levels and metabolic syndrome. The study results showed that the prevalence of metabolic syndrome and its components augmented with the increasing levels of uric acid in both sexes. The adjusted OR for having metabolic syndrome per 1.0mg/dL higher uric acid concentration for males and females were 1.16 and 1.27, respectively. There was an association identified between metabolic syndrome and hyperuricemia with adjusted odds ratios of 1.71 and 1.55 in both the males and women, respectively. The study concluded that the elevated SUA concentration itself-reliantly related with an increased occurrence of metabolic syndrome.

Cicero AFG et al[40], conducted a study of 923 individuals. The study aimed to evaluate the association between SUA concentrations and the prevalence of metabolic syndrome. The study results found that metabolic syndrome was more common for higher serum uric acid concentrations. Serum uric acid was predictive of MS in the whole population and both sex subgroups. The best cut-off values for the men and women were 5.5 mg/dl and 4.2 mg/dl, respectively. Also, SUA appeared predictive of middle-term metabolic syndrome incidence in the whole population and the female group. The study concluded that serum uric acid is one of the frequency components of metabolic syndrome.

Foster C et al[41], conducted a retrospective study. The objective of this study was to identify the relationship among SUA and markers of insulin resistance and low-grade inflammation in obese adolescents with and without metabolic syndrome. The study results revealed that 41.8% of the participants were identified with hyperuricemia. FM, SBP, HbA1c, insulin and HOMA-IR were higher in adolescents with HUA. There was a positive correlation between SUA, FM, SBP, HOMA-IR and HbA1c and triglyceride: HDL-C ratio. Around 32.8% was identified with metabolic syndrome. FM, SBP, DBP, SUA, ALT, insulin, HOMA-IR, and TG: HDL-c ratio were significantly higher with the presence of the metabolic syndrome. There was a positive correlation identified between FM, serum uric acid, HOMA-IR and hs-CRP. The study concluded that SUA is correlated with metabolic syndrome comorbidities.

Huang S et al[42], performed a study in 1,903 people. This aim of the study was to determine the association between SUA, metabolic syndrome and its components. The study results revealed that 21.0% and 17.1% were the prevalence of hyperuricemia and metabolic syndrome. There was a positive correlation identified between serum uric acid, waist circumference, body mass index and triglycerides. Whereas, a negative correlation with high-

density lipoprotein cholesterol in both sexes. Both males and females with high SUA quartile had a higher risk of MS. Similarly, the risk of central obesity, high blood pressure and hypertriglyceridemia compared to the lowest serum uric acid quartile were also high in individuals with higher serum uric acid levels. The study concluded that SUA is closely related to the development of the metabolic syndrome.

Klisic A et al[43], performed a cross-sectional study in 83 patients. This study evaluated the xanthine oxidase and uric acid as independent predictors of albuminuria in patients with diabetes mellitus type 2. The study results showed that the independent predictors for albuminuria onset in subjects with DM2 were the uric acid and XO. The probability for albuminuria was increased by 1.5% with 1 μmol/L of the rise in uric acid. The study concluded that the XO and uric acid are independently associated with albuminuria in diabetes.

Li X et al[44], performed a Prospective Cohort Study in 4,412 participants. This study determined the role of xanthine oxidase in the development ofT2DM. The study results showed that the novel-onset T2DM was identified in 249 female and 360 men, respectively. There was a positive correlation recognized between serum XO activity and UA concentration. XO activity was significantly related to the prevalence of T2DM. This study showed that elevated serum XO activity was associated with an increased risk of developing T2DM.

Sunagawa S et al[45], conducted a study in 60 patients. This study evaluated the activity of xanthine oxidase in plasma with indices of insulin resistance and liver dysfunction in patients with type 2 DM and metabolic syndrome. There was a correlation identified between the value of plasma XO activity, indices of IR and the level of circulating liver transaminases.

Whereas, indices of insulin resistance, the value of plasma XO activity were not correlated with the serum uric acid level. The study concluded that the Plasma XO activity correlates with indices of insulin resistance and liver dysfunction in patients with T2D and MetS.

Viazzi F et al[46], conducted a study in 2429 patients. The objective of the study was to find the relationship between serum uric acid, metabolic syndrome and other cardiovascular risk factors in hypertensive patients with a high prevalence of diabetes. The mean age of the participants was 62 ± 11 years. The study results that 72%, 43%, and 20% were the prevalence of MS, CKD and positive history for CV events. There was a correlation identified between SUA levels, the presence of metabolic syndrome, its components, signs of renal damage and worse CV risk profile. There was an association observed between serum uric acid, a positive history of CV events and high Framingham risk score. The study concluded the mild hyperuricemia is a strong, independent marker of MS and high cardio-renal risk profile in hypertensive patients.

Wang H-J et al[47], performed a study in 468 women. This study aimed to identify the connotation between uric acid and metabolic syndrome in elderly women. The study results showed that the people in the second, third and fourth quartile of uric acid showed 2.23-fold, 2.25-fold and 4.41-fold increased risk for the metabolic syndrome. Similarly, each 1 mg/dl augmentation of SUA level showed 1.38-fold times increased risk for metabolic syndrome. The study concluded that elevated uric acid is positively associated with the occurrence of metabolic syndrome in elderly women.

Yadav D et al[48], conducted a study in 1590 adults. This study aimed to assess whether serum uric acid foresees new onset of metabolic syndrome. The study results revealed that 16.4

percent of the participants developed metabolic syndrome during the period of follow up. There was connotation identified between MS variables and baseline serum uric acid level. The participants in the quintile of SUA were identified with higher waist circumference, blood pressure and serum triglyceride. Total cholesterol and low-density lipoprotein cholesterol in men and women, individuals in the fifth quintiles of serum uric acid were identified with higher ORs for incident MS. In women, the association between hyperuricemia and new onset of metabolic syndrome were identified as stronger as compared to men. The study concluded that serum uric acid can be correlated with the future risk of WC, BP, TG and can also predicted as a risk factor for developing MetS

Yang T et al[49], performed a prospective cohort study in 3857 subjects. This study aimed to identify the role of uric acid in metabolic syndrome. The study results revealed that 476 participants developed metabolic syndrome during the time of follow up. There was an increase in the incidence of metabolic syndrome across tertiles of serum uric acid in the study population. The risk of developing MS was higher in the participants with variations of blood pressure, HDL-C, triglycerides, glucose, and waist circumference, females in the middle and upper tertiles of SUA. The independent risk determinant for metabolic syndrome in women was identified as hyperuricemia. The study concluded that SUA concentration is more closely related to metabolic syndrome in females as compared to males.

You L et al[50], conducted a cross-sectional study in 1,426 subjects. This study determined the incidence of hyperuricemia and the connotation between the SUA levels and incidence of metabolic syndrome. The study results revealed that 17.7% and 5.2% were the prevalence of hyperuricemia in males and females. The frequency of metabolic syndrome in men and women were 36.7% and 5.2% respectively. There was a correlation recognized between waist

circumference, BMI, the level of triglycerides and SUA levels. The risk of MetS was high in men with hyperuricemia. While the risk of MetS, central obesity and hypertriglyceridemia were greater in men with a normal serum uric acid level. Likewise, risk of MS, central obesity, hypertriglyceridemia and hypertension were greater in women with a higher serum uric acid level. The study concluded that individuals with a normal level of SUA had an augmented risk of metabolic syndrome and other metabolic disorders.

Yuan H et al[51], conducted a meta-analysis. The study aimed to find the correlation between the SUA levels and the metabolic syndrome risk. The study results revealed that a combined RR of 1.72 was identified for the highest serum uric acid level category. Increase in SUA concentration by 1mg/Dl increased risk of MS. Similarly, each 1 mg/dL serum uric acid level increment can increase the risk of NAFLD by 21%. The study concluded that increased SUA levels can led to an increased risk of MS.

Zhang H et al[52], conducted a meta-analysis study in 16,577 subjects. This study objective was to find the connotation between SUA and metabolic syndrome. The study results revealed that there was an increase in MS with the increasing SUA concentration in both sexes. The adjusted ORs of metabolic syndrome comparing the fourth and firstly quartiles in men and women were 3.11 and 3.64, respectively. Increase in SUA concentration by 1mg/Dl increased the risk of MS in men and women by 41% and 62% respectively. The study concluded that SUA concentration is positively correlated with the prevalence of metabolic syndrome.

Zurlo A et al[53], conducted a study in a prospective cohort study in 1128 participants. The study results showed that the mean SUA level in men and women were 5.4 ± 1.2 and 4.5 ± 1.2 mg/dl, respectively. Metabolic syndrome was developed in 496 individuals during

the period of follow up. Women with serum uric acid levels more than 1 SD above the mean ≥5.7 mg/dl was identified with a higher risk of developing metabolic syndrome. The study concluded that high SUA levels are an independent predictor of metabolic syndrome in older women.

LACUNAE OF LITERATURE:

Previous studies have explored the connotation between SUA, XO and metabolic syndrome. Still, evidence on the strength and consistency of the connotation remains uncertain and limited, especially in the rural population. Besides, the epidemiological research and meta-analysis on the association have not been reported. Similarly, few studies have focused on elderly populations. The available data regarding the cause and effect relationship between Serum uric acid and Xanthine oxidase in metabolic syndrome individuals remains limited in studies.

MATERIALS & METHODS

MATERIALS&METHODS:

Study site: This study was conducted in the Department of General medicine at R.L. JALAPPA hospital, SRI DEVRAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR

Study population: All the Patients attending the outpatient and inpatient of Department of General medicine at R.L. JALAPPA hospital, SRI DEVRAJ URS MEDICAL COLLEGE were considered as the study population.

Study Design: This study was a cross-sectional observational study**.**

Sample size:

Sample size estimated based on the difference in Uric Acid levels in a case study by Sara Nejatinamini et al[54,] in 2015, which reported an average variance estimate of (Standard Deviation=1.46), with 5% alpha error with 80% power with an effect size of 0.5(expecting an increase of 14.6% in uric acid levels) the estimated sample size for the case is 64.

The total sample size is 128 (64 cases + 64 control)

Sample Size Estimation Formula:

$$\text{Sample size} = \frac{2SD^2(Z_{\alpha/2}+Z_{\beta})^2}{d^2}$$

SD – Standard deviation = From previous studies or pilot study

$Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ (From Z table) at type 1 error of 5%

$Z_{\beta} = Z_{0.20} = 0.842$ (From Z table) at 80% power

d = effect size = difference between mean values

So now formula will be

$$\text{Sample size} = \frac{2SD^2(1.96+0.84)^2}{d^2}$$

Sampling method: All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

Study Duration: The study was carried out over 18 months from January 2019 to July 2020.

Inclusion criteria:

- Individuals above 18 years of age.

CASES:

According to IDF criteria for metabolic syndrome[3]: -

Central obesity – defined as waist circumference ≥ 90cm for men and ≥80 cm for women (Indian population)

Plus, any two of the following four factors: -

- Hypertriglyceridemia: Triglycerides >150 mg/dL or on specific medication.
- Low HDL cholesterol: <40 mg/dL and <50 mg/dL in men and women respectively, or on specific medication.
- Hypertension: Blood pressure >130 mm systolic or >85 mm diastolic or on specific medication.
- Fasting plasma glucose: ≥100 mg/dL or specific medication or previously diagnosed type 2 Diabetes Mellitus / Impaired fasting glucose/ impaired glucose tolerance.

CONTROL: Individuals who do not meet the IDF criteria for Metabolic Syndrome.

Exclusion criteria:

- Hepatocellular carcinoma, Breast cancer.
- Severe renal insufficiency.
- Patient on hemodialysis.
- Chronic alcohol consumption.
- Drugs - antiepileptics, OCPs, erythromycin, trimethoprim, sulphamethoxazole, cimetidine, allopurinol, cyclosporine, pyrazinamide, ethambutol, levodopa uricosuric drugs, anti tubercular drugs.

- Gout.

Ethical considerations: Study was approved by the institutional human ethics committee. Informed written consent was obtained from all the study participants, and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

Data collection tools: All the relevant parameters were documented in a structured study proforma.

Methodology:

After obtaining Ethical committee approval, the study participants were careened for Metabolic syndrome based on the IDF criteria. Written informed consent was taken from all the study groups.

For the study, the following operational standard criteria/definitions were used:

- BMI calculated as - weight in kg/height in m^2
- Blood pressures were recorded after at least 5 minutes of rest in both arms sitting/supine position.

Waist circumference- measured in a horizontal plane midway between the inferior margin of the ribs and superior border of the iliac crest by using a standard measuring tape.

Blood sample collection and analysis:

After explaining the procedure, under aseptic precautions, 2 ml of venous blood was collected in EDTA tube, and 2ml of venous blood is collected in plain tube. For FBS, 2 ml of venous sample was collected after 8-10 hours of overnight fasting.

EDTA blood was used for the estimation of complete Hemogram. Blood in the plain tube was allowed to clot for 10 minutes at room temperature. Serum was separated after centrifuge at 3000rpm for 10 minutes. The serum is used for the estimation of the following parameters. Fasting Blood Sugar, Total Cholesterol, Triglycerides, HDL cholesterol and Serum uric acid. All the parameters were analyzed by using standard methods in Vitros 5.1 FS dry chemistry analyzer. Xanthine Oxidase activity is measured by ELISA kit.

Statistical Methods:

Metabolic syndrome was considered as the outcome variable. Uric Acid and Serum xanthine oxidase was considered as a primary explanatory variable.

Age, gender, co-morbidities, etc. were considered as a secondary explanatory variable.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. All Quantitative variables were checked for normal distribution within each category of an explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro- wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as a normal distribution.

For customarily distributed Quantitative parameters, the mean values were compared between study groups using Independent sample t-test (2 groups). The association between the study group and categorical outcomes was assessed by cross tabulation and comparison of percentages. Chi square test was used to test statistical significance. Data was also

represented using appropriate diagrams like a bar diagram, pie diagrams and clustered bar charts, etc.

The utility of uric acid and Serum xanthine oxidase in predicting metabolic syndrome was assessed by Receiver Operative curve (ROC) analysis. The area under the ROC curve along with its 95% CI and p value are presented. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening test with the decided cut off values along with their 95% CI were presented.

P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[55]

OBSERVATIONS AND RESULTS

RESULTS:

A total of 128 participants were included in the final analysis with 64 participants in with metabolic syndrome and 64 participants without metabolic syndrome.

Table 3: Descriptive analysis of age in the study population (N=128)

Parameter	Mean ± S. D	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Age	55.64±12.61	56.00	21.00	84.00	53.44	57.83

The mean age of participants was 55.64±12.61 years in the study population, with 21 years being the minimum age and 84 years being the maximum age. (Table 3)

Table 4: Descriptive analysis of gender in the study population (N=128)

Gender	Frequency	Percentage
Female	49	38.28%
Male	79	61.72%

Among the study population, 49 (38.28%) participants were male, and 79 (61.72%) participants were female. (Table 2)

Table 5: Descriptive analysis of co-morbidities in the study population (N=128)

Co-morbidities	Frequency	Percentage
Hypertension	57	44.53%
Type 2 Diabetes Mellitus	59	46.09%

Among the study population, 57 (44.53%) participants had hypertension, and 59 (46.09%) subjects had type 2 diabetes mellitus. (Table 5 & Figure 5)

Figure 5: Pie chart for comorbidities in the study population (N=128)

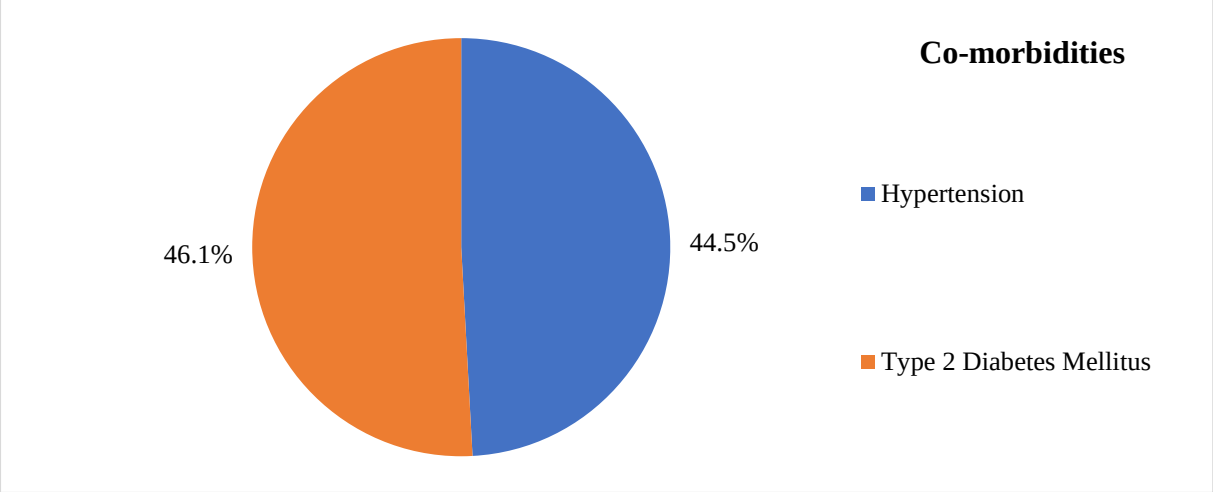


Table 6: Descriptive analysis of metabolic syndrome in the study population (N=128)

Metabolic syndrome	Frequency	Percentage
Yes	64	50.00%
No	64	50.00%

Among the study population, 64 (50.00%) subjects had metabolic syndrome, and 64 (50.00%) participants didn't have metabolic syndrome. (Table 6 & Figure 6)

Figure 6: Bar chart for metabolic syndrome in the study population (N=128)

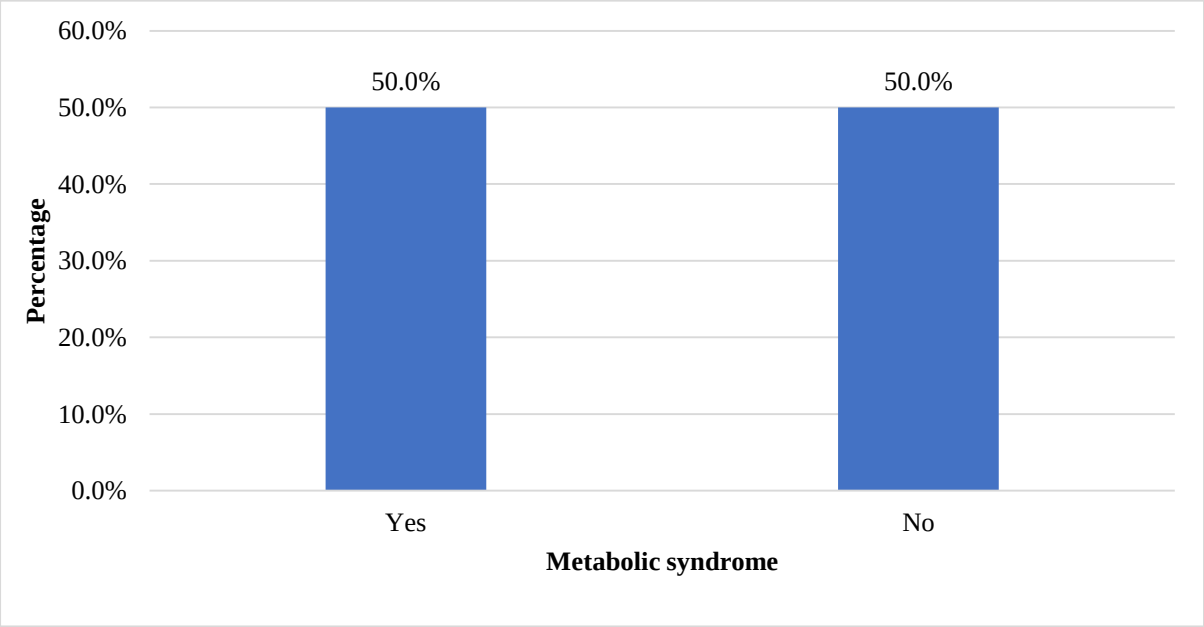


Table 7: Descriptive analysis of clinical parameters in the study population (N=128)

Parameters	Mean ± S. D	Median	Minimum	Maximum	95% CI	
					Lower CI	Upper CI
Fasting Blood Sugar(100mg/dl) (N=128)	133.47±80.53	98.00	62.00	432.00	119.47	147.48
High-density lipoproteins (mg/dl)	44.73±10.19	44.00	20.00	63.00	42.97	46.50
Waist circumference	90.71±10.29	90.00	62.00	121.00	88.93	92.49
Serum xanthine oxidase (U /mg) (N=128)	2.02±1.22	1.90	0.40	5.10	1.80	2.23
Uric acid (mg/dl)	7.24±0.74	7.30	5.20	9.60	7.11	7.37

Among the study population, mean Fasting Blood Sugar was 133.47±80.53 mg/dl (ranged from 62 mg/dl to 432 mg/dl), mean HDL (High-density lipoproteins) was 44.73±10.19 mg/dl (ranged from 20 mg/dl to 63 mg/dl), mean waist circumference was 90.71±10.29 cm (ranged from 62 units to 121 units), mean serum xanthine oxidase was 2.02±1.22 U/mg (ranged from 0.40 U/mg to 5.10 U/mg) and mean Uric acid was 7.24±0.74 mg/dl (ranged from 5.20 mg/dl to 9.60 mg/dl). (Table 7)

Table 8: Comparison of mean age(years) between metabolic syndrome (N=128)

Parameter	Metabolic syndrome (Mean± SD)		P value
	Yes (N=64)	No (N=64)	
Age	58.22 ± 11.16	53.02 ± 13.52	0.020

Among the study population, the mean age of subjects with metabolic syndrome was 58.22 ± 11.16 years, and without metabolic syndrome was 53.02 ± 13.52 years. The mean difference of age among the groups was statistically significant (P Value<0.001). (Table 8)

Table 9: Comparison of baseline parameters between metabolic syndrome (N=128)

Parameters	Metabolic Syndrome		Chi square	P value
	Yes	No		
Gender				
Male (N=79)	38 (48.1%)	41 (51.9%)	0.298	0.585
Female (N=49)	26 (53.06%)	23 (46.94%)		
Type 2 Diabetes Mellitus				
Yes (N=59)	50 (84.75%)	9 (15.25%)	52.854	<0.001
No (N=69)	14 (20.29%)	55 (79.71%)		
Hypertension				
Yes (N=57)	36 (63.16%)	21 (36.84%)	7.116	0.008
No (N=71)	28 (39.44%)	43 (60.56%)		

Out of 79 male participants, 38 (48.1%) participants had metabolic syndrome, while 41 (51.9%) participants did not have metabolic syndrome. Out of 49 female participants, 26 (53.06%) participants had metabolic syndrome, while 23 (46.94%) participants did not have metabolic syndrome. The difference in the proportion of gender between metabolic syndrome was statistically not significant (P Value>0.05). Out of 59 participants with type 2 diabetes mellitus, 50 (84.75%) participants had metabolic syndrome, while 9 (15.25%) participants did not have metabolic syndrome. Out of 69 participants without type 2 diabetes mellitus, 14 (20.29%) participants had metabolic syndrome, while 55 (79.71%) participants did not have metabolic syndrome. The difference in the proportion of type 2 diabetes mellitus between the metabolic syndrome was statistically not significant (P Value<0.05). Out of 57 participants with hypertension, 36 (63.16%) participants had metabolic syndrome, while 21 (36.84%) participants did not have metabolic syndrome. Out of 71 participants without hypertension, 28 (39.44%) participants had metabolic syndrome, while 43 (60.56%) participants did not

have metabolic syndrome. The difference in the proportion of hypertension between metabolic syndrome was statistically not significant (P Value<0.05). (Table 9 & Figure 7)

Figure 7: Comparison of co-morbidities between metabolic syndrome (N=128)

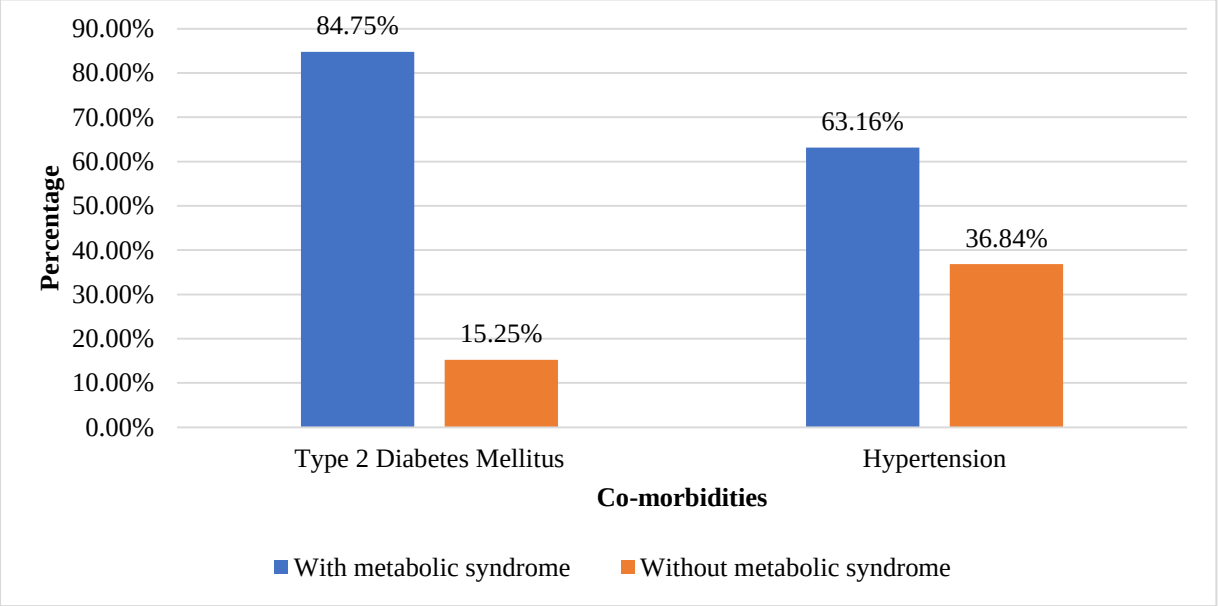


Table 10: Comparison of mean clinical parameters between metabolic syndrome (N=128)

Parameter	Metabolic syndrome (Mean± SD)		P value
	Yes (N=64)	No (N=64)	
Fasting Blood Sugar(100mg/dl) (N=128)	172.21 ± 87.42	95.34 ± 49.71	<0.001
Uric acid (mg/dl) (N=128)	7.58 ± 0.74	6.9 ± 0.58	<0.001
Serum xanthine oxidase (U /mg) (N=128)	2.99 ± 0.91	1.08 ± 0.55	<0.001

Among the study population, Fasting Blood Sugar was 172.21 ± 87.42 mg/dl for participants with metabolic syndrome and it was 95.34 ± 49.71 mg/dl for participants without metabolic syndrome, Uric acid was 7.58 ± 0.74 mg/dl for participants with metabolic syndrome, and it was 6.9 ± 0.58 mg/dl for participants without metabolic syndrome, and Serum xanthine oxidase was 2.99 ± 0.91 U/mg for participants with metabolic syndrome and it was 1.08 ± 0.55 U/mg for participants without metabolic syndrome. The difference in mean of all the

clinical parameters was statistically significant between the metabolic syndrome (P Value<0.05). (Table 10)

Table 11: Comparison of high-density lipoproteins for males and females between metabolic syndrome (N=128)

High-density lipoproteins (mg/dl)	Metabolic Syndrome		Chi square	P value
	Yes (N=64)	No (N=64)		
For Females (N=49)				
<50 (N=33)	24 (92.31%)	9 (39.13%)	15.693	<0.001
≥50 (N=16)	2 (7.69%)	14 (60.87%)		
For Males (N=79)				
<40 (N=32)	31 (81.58%)	1 (2.44%)	51.255	<0.001
≥40 (N=47)	7 (18.42%)	40 (97.56%)		

In female participants with metabolic syndrome, 24 (92.31%) participants had HDL <50 mg/dl and 2 (7.69%) participants had HDL ≥50 mg/dl. In female participants without metabolic syndrome, 9 (39.13%) participants had HDL <50 mg/dl and 14 (60.87%) participants had HDL ≥50 mg/dl. In male participants with metabolic syndrome, 31 (81.58%) participants had HDL <40 mg/dl and 7 (18.42%) participants had HDL ≥40 mg/dl. In male participants without metabolic syndrome, 1 (2.44%) participant had HDL <40 mg/dl and 40 (97.56%) participants had HDL ≥40 mg/dl. The difference in proportion of female HDL and male HDL between metabolic syndrome was statistically significant (P Value<0.05). (Table 11)

Table 12: Comparison of waist circumference for males and females between metabolic syndrome (N=128)

Waist Circumference	Metabolic Syndrome		Chi square	P value
	Yes (N=64)	No (N=64)		
For Females (N=49)				
<80cm (N=13)	0 (0%)	13 (56.52%)	*	*
≥80cm (N=36)	26 (100%)	10 (43.48%)		
For Males (N=79)				
<90 (N=26)	0 (0%)	23 (56.1%)	*	*
≥90 (53)	38 (100%)	18 (43.9%)		

**No statistical test was applied due to 0-subjects in one of the cells.*

In female participants with metabolic syndrome, no participants had Waist Circumference<80cm and 26 (100%) participants had Waist Circumference ≥ 80cm. In female participants without metabolic syndrome, 13 (56.52%) participants had Waist Circumference <80cm and 10 (43.48%) participants had Waist Circumference ≥ 80cm. In male participants with metabolic syndrome, no participants had Waist Circumference < 90cm and 38 (100%) participants had Waist Circumference ≥ 90cm.

Figure 8: Predictive validity of uric acid in predicting metabolic syndrome (N=128)

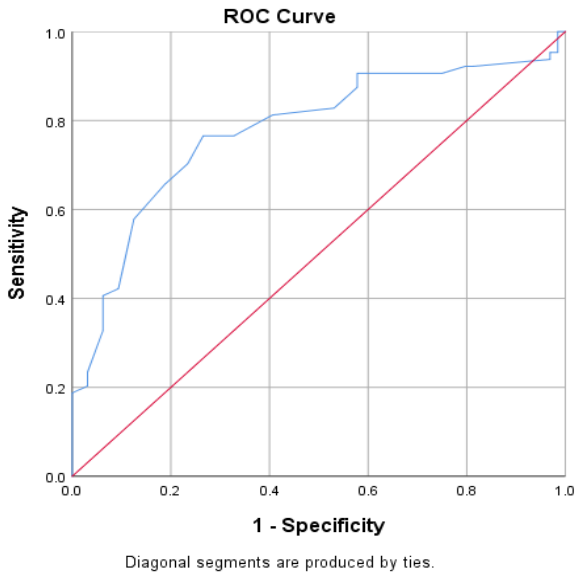


Table 13: Area under the curve for the predictive validity of uric acid in predicting metabolic syndrome (N=128)

Test Result Variable(s): Uric Acid in metabolic syndrome				
Area Under the Curve	Std. Error	95% Confidence Interval of AUC		**P Value**
		Lower Bound	Upper Bound	
0.778	0.042	0.695	0.861	<0.001

The Uric acid had good predictive validity in predicting metabolic syndrome, as indicated by the area under the curve of 0.778 (95% CI 0.695 to 0.861, P value <0.001). (Table 13 & Figure 8)

Table 14: Comparison of uric acid between metabolic syndrome (N=128)

Uric Acid (mg/dl)	**Metabolic Syndrome**		**Chi square**	**P value**
	Yes (N=64)	**No (N=64)**		
≥7.35	45 (70.31%)	15 (23.44%)	28.235	<0.001
<7.35	19 (29.69%)	49 (76.56%)		

Out of 64 participants with the presence of Metabolic Syndrome, the Uric Acid was ≥7.35 mg/dl for 45 (70.31%) participants while it was <7.35 mg/dl for 19 (29.69%) participants.

Out of 64 participants without Metabolic Syndrome, the Uric Acid was ≥7.35 mg/dl for 15 (23.44%) participants while it was <7.35 mg/dl for 49 (76.56%) participants. The difference in the proportion of uric acid between metabolic syndrome was statistically significant (P value<0.05). (Table 14 & Figure 9)

Figure 9: Clustered bar chart for comparison of uric acid between metabolic syndrome (N=128)

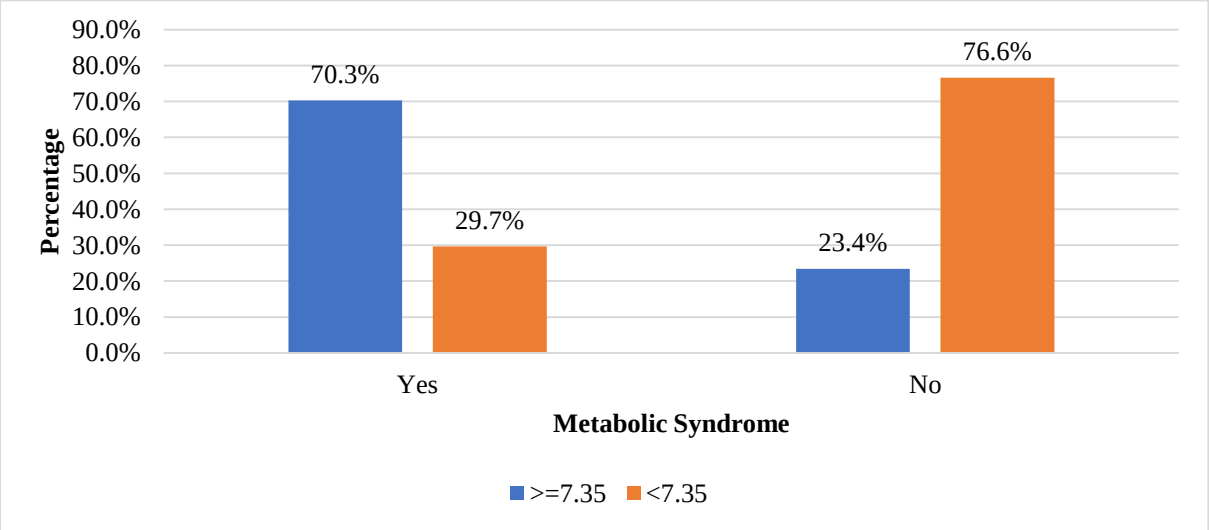


Figure 10: Predictive validity of serum xanthine oxidase (U /mg) in predicting metabolic syndrome (N=128)

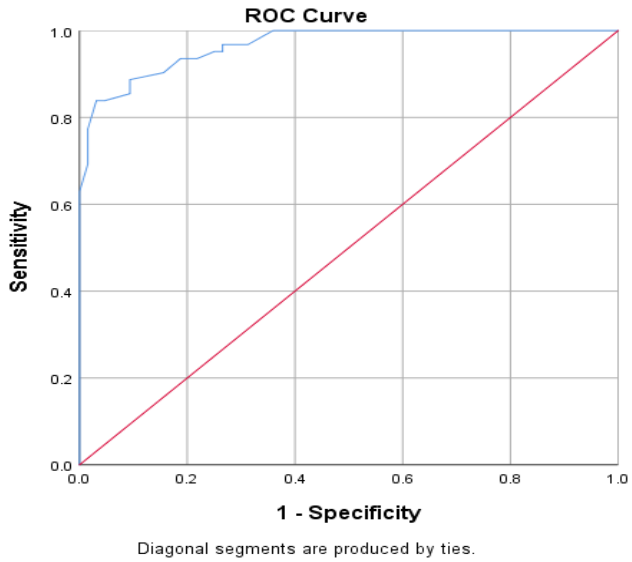


Table 15: Area under the curve for the predictive validity of serum xanthine oxidase (U /mg) in predicting metabolic syndrome (N=128)

Test Result Variable(s): Serum xanthine oxidase (U /mg) in metabolic syndrome				
Area Under the Curve	Std. Error	95% Confidence Interval of AUC		**P Value**
		Lower Bound	Upper Bound	
0.966	0.013	0.941	0.991	<0.001

The Serum xanthine oxidase had excellent predictive validity in predicting metabolic syndrome, as indicated by the area under the curve of 0.966 (95% CI 0.941 to 0.991, P value <0.001). (Table 15 & Figure 10)

Table 16: Comparison of serum xanthine oxidase (U /mg) between metabolic syndrome (N=128)

Serum xanthine oxidase (U /mg)	**Metabolic Syndrome**		**Chi square**	**P value**
	Yes (N=64)	**No (N=64)**		
≥1.95	55 (88.71%)	6 (9.38%)	75.196	<0.001
<1.95	9 (11.29%)	58 (90.63%)		

Out of 62 participants with the presence of Metabolic Syndrome, the Serum xanthine oxidase was ≥1.95 U/mg for 55 (88.71%) participants while it was <1.95 U/mg for 7 (11.29%) participants. Out of 64 participants without Metabolic Syndrome, the Serum xanthine oxidase was ≥1.95 U/mg for 6 (9.38%) participants while it was <1.95 U/mg for 58 (90.63%) participants. The difference in the proportion of Serum xanthine oxidase between metabolic syndrome was statistically significant (P value<0.05). (Table 16 & Figure 11)

Figure 11: Clustered bar chart for comparison of serum xanthine oxidase (U /mg) between metabolic syndrome (N=128)

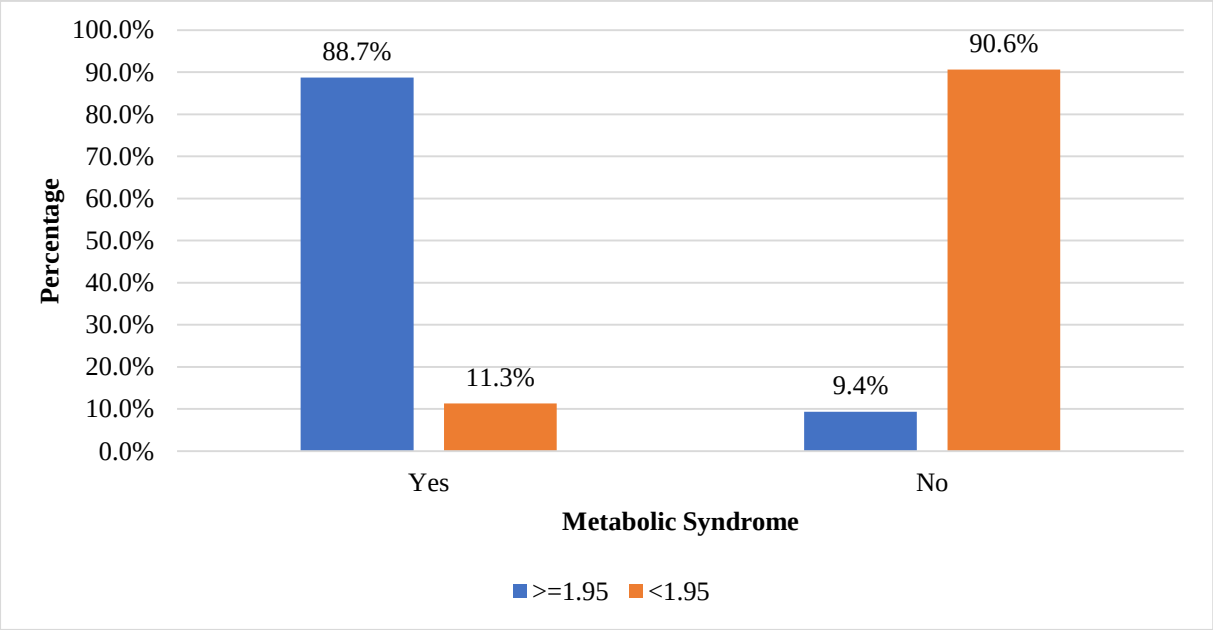


Table 17: Predictive validity of uric acid and serum xanthine oxidase in predicting metabolic syndrome (N=128)

Parameter	Uric Acid Value (95% CI)	Serum xanthine oxidase Value (95% CI)
Sensitivity	70.31% (57.58%-81.09%)	88.71% (78.11%-95.34%)
Specificity	76.56% (64.31%-86.25%)	90.63% (80.70%-96.48%)
False positive rate	23.44% (13.75%-35.69%)	9.38% (3.52%-19.30%)
False negative rate	29.69% (18.91%-42.42%)	11.29% (4.66%-21.89%)
Positive predictive value	75.00% (62.14%-85.28%)	90.16% (79.81%-96.30%)
Negative predictive value	72.06% (59.85%-82.27%)	89.23% (79.06%-95.56%)
Diagnostic accuracy	73.44% (64.91%-80.85%)	89.68% (83.00%-94.39%)
Positive likelihood ratio	3.00 (1.71-4.478)	9.46 (4.14-19.096)
Negative likelihood ratio	0.39 (0.05-0.579)	0.12 (0.02-0.251)

The uric acid had sensitivity of 70.31% (95% CI 57.58% to 81.09%) in predicting presence of metabolic syndrome. Specificity was 76.56% (95% CI 64.31% to 86.25%), false positive rate was 23.44% (95% CI 13.75% to 35.69%), false negative rate was 29.69% (95% CI 18.91% to

42.42%), positive predictive value was 75.00% (95% CI 62.14% to 85.28%), negative predictive value was 72.06% (95% CI 59.85% to 82.27%), and the total diagnostic accuracy was 73.44% (95% CI 64.91% to 80.85%). The Serum xanthine oxidase had sensitivity of 88.71% (95% CI 78.11% to 95.34%) in predicting presence of metabolic syndrome. Specificity was 90.63% (95% CI 80.70% to 96.48%), false positive rate was 9.38% (95% CI 3.52% to 19.30%) false negative rate was 11.29% (95% CI 4.66% to 21.89%), positive predictive value was 90.16% (95% CI 79.81% to 96.30%), negative predictive value was 89.23% (95% CI 79.06% to 95.56%), and the total diagnostic accuracy was 89.68% (95% CI 83.00% to 94.39%). (Table 17)

DISCUSSION

DISCUSSION:

ROLE OF XANTHINE OXIDASE AND URIC ACID IN METABOLIC SYNDROME

Worldwide, the incidence of obesity and metabolic syndrome is rapidly increasing. It leads to an increased rate of mortality and morbidity.[3, 56] Insulin resistance, adipose tissue dysfunction, chronic inflammation, oxidative stress, circadian disruption, microbiota, genetic factors, and maternal programming are the major contributing factors and mechanisms involved in the metabolic syndrome.[9]

Xanthine oxidoreductase can be a contributor to the pathogenesis of metabolic syndrome through the oxidative stress and the inflammatory response induced by XOR-derived reactive oxygen species and uric acid. Hyperuricemia is closely associated with hypertension, insulin resistance, obesity and hypertriglyceridemia.

Patients with metabolic syndrome, are at a high risk of developing diabetes and CVD; therefore, early intervention, primarily lifestyle modifications can ultimately prevent these costly and deadly diseases. The present study was directed to determine the role of xanthine oxidase and uric acid in metabolic syndrome.

A total of 128 participants were involved in the study.

In the present study, 55.64±12.61 years was identified as the mean age of the study population. Bonakdaran S et al[37], conducted a cross-sectional study in 100 participants in which the mean age of the subjects was noticed as 59 years which is slightly higher to our study results.

In the present study, the majority of the participants were females, with 61.72% followed be males with 38.28%. Chen LY et al[34], showed a conflicting result as compared to our study in which 61.84% of participants were males and remaining 38.16% females.

In the current study, the majority of the participants (46.09%) had type 2 DM as comorbidity, followed by hypertension with 44.53%. Bonakdaran S et al[37], conducted a cross-sectional study in which most of the participants had T2D and hypertension with 70% and 26.17% respectively.

In the current study, MetS was identified in 50% of the participants. Foster C, et al[41], in a retrospective study in which 30% of the subjects had metabolic syndrome, which is a declined rate as compared to our study results.

In the present study, the mean of Fasting Blood Sugar, HDL, waist circumference, Serum xanthine oxidase and Uric acid were identified with 133.47±80.53 mg/dl, 44.73±10.19 mg/dl, 90.71±10.29 units, 2.02±1.22 U/mg and .24±0.74 mg/dl respectively. Cicero AFG et al[40], conducted a study in 923 subjects in which the mean of fasting blood sugar, HDL, WC and uric acid were noticed with 100.8 ± 9.6md/dl, 46.5 ± 9.7mg/dl, 89.2± 12.1 cm and 4.8 ± 1.4 mg/dl respectively.

In the present study, 58.22 ± 11.16 years and 53.02 ± 13.52 years were identified as the mean age of participants with MetS and without MetS. In a cross-sectional study performed Bonakdaran S. et al[37], by in 100 participants in which the mean age of participants with the metabolic syndrome and without MetS was noticed with 59.55 years and 55.8 years which is similar to our study results.

Table 18: Comparison of mean age between metabolic syndrome in various studies.

Study	Population	Mean of age
Present study	128	With MetS (58.22 ± 11.16) Without MetS (53.02 ± 13.52)
Chen D et al.[40]	3675	With MetS (47.24 ± 12.58) Without MetS (37.94± 12.16)

Out of 79 male participants, the metabolic syndrome was observed in 48.1% Similarly, out of 49 female participants, 53.06% of participants had metabolic syndrome. Bonakdaran S et al[37], conducted a study in which metabolic syndrome was identified in 60% of male participants and 40% of female subjects which is conflicting to our study results.

Out of 59 participants with type 2 diabetes mellitus, 84.75% of participants had metabolic syndrome Whereas, out of 69 participants without type 2 diabetes mellitus, 20.29% of participants had metabolic syndrome.

Out of 57 participants with hypertension, 63.16% of subjects had metabolic syndrome. Similarly, out of 71 participants without hypertension, 39.44% of participants had metabolic syndrome. In a cross-sectional study performed by Bonakdaran S et al[37], in 100 participants in which 25.71 of participants with hypertension had MS while 26.67 of participants without hypertension had metabolic syndrome which is contradictory to our study results.

In the present study, fasting blood sugar, uric acid and serum xanthine oxidase were identified with 172.21 ± 87.42mg/dl, 7.58 ± 0.74 mg/dl and 2.99 ± 0.91 U/mg in participants with the metabolic syndrome. Jeong J et al[57], conducted a study in 5,758 subjects in which fasting blood sugar and uric acid were identified with 115.56 ± 0.94mg/dl and 5.58 ± 0.04mg/dl respectively which is contradictory to our study results.

In the current study, high-density lipoproteins were <50 mg/dl in the majority of female participants with metabolic syndrome Similarly it was less than 40 mg/dl in the majority of

male patients with metabolic syndrome. Woldeamlak B. et al[58], conducted a cross-sectional study in 384 participants in which the HDL (mg/dl) was l0w in 20% of participants which is a decreased rate as compared to our study results.

In the present study, all the female subjects with metabolic syndrome had WC ≥ 80cm. Whereas, the majority of male participants with metabolic syndrome had Waist Circumference ≥90cm. In Woldeamlak B., et al[58], study the waist circumference was high in 24% of patients which is a decreased rate as compared to our study.

In the present study, the Uric Acid was ≥ 7.35 for 70.31% participants with metabolic syndrome. Woldeamlak B. et al[58], conducted a cross-sectional study in 384 participants in which hyperuricemia was recognized in 31.05% of patients which is a reduced proportion as compared to our study.

In the current study, the level of serum xanthine oxidase was ≥ 1.95 for 88.71% of participants. In the present study, the uric acid had sensitivity, specificity, false positive rate, false-negative rate, positive predictive value, negative predictive value and total diagnostic accuracy of 70.31%, 76.56%, 23.44%, 29.69%, 75%, 72.06% and 73.44% in predicting the presence of the metabolic syndrome. Similarly, the serum xanthine oxidase had sensitivity, specificity, false positive rate, false-negative rate, positive predictive value, negative predictive value and total diagnostic accuracy of 88.71%, 90.63%, 9.38%, 11.29%, 90.16%, 89.23% and 89.68% in predicting the presence of the metabolic syndrome.

The present study indicated that the uric acid and serum xanthine oxidase had a good predictive value in predicting the metabolic syndrome.

CONCLUSION:

In conclusion, the present study showed a strong association between uric acid, xanthine oxidase and prevalence of metabolic syndrome. It also indicates that the waist circumference, uric acid, serum xanthine oxidase and HDL levels can indicate the risk of developing metabolic syndrome.

Physicians should recognize metabolic syndrome as a common comorbidity of hyperuricemia and take immediate action to prevent subsequent chronic disease and related potential socioeconomic problem.

LIMITATIONS:

One of the major limiting factors in the present study is the small sample size and short duration of the study.

RECOMMENDATIONS:

The use of some medications, such as a statin, angiotensin receptor blocker, and fibrate, can affect the level of serum uric acid. Therefore, further longitudinal studies that include factors that might influence this association are needed to investigate the directionality of the link between uric acid and metabolic syndrome.

SUMMARY:

Metabolic syndrome is a multifactorial pathological condition defined by the association of several metabolic disorders. The visceral obesity, dyslipidemia with high triglycerides or low level of high-density lipoprotein cholesterol, hypertension and fasting hyperglycemia are included in metabolic disorders. Hyperuricemia is closely associated with hypertension, insulin resistance, obesity and hypertriglyceridemia. There is a correlation identified between the serum level of XOR, high-density lipoprotein and fasting glycemia,

Patients with metabolic syndrome, are at a high risk of developing diabetes and CVD; therefore, early intervention, primarily lifestyle modifications can ultimately prevent these costly and deadly diseases. The present study was conducted to determine the role of xanthine oxidase and uric acid in MetS.

A total of 128 participants were enrolled in the study. The mean age of participants was 55.64±12.61 years. Majority of the participants in the study population were males with 61.72%. Hypertension and type 2 DM were identified with 44.53% and 46.09% respectively. Metabolic syndrome was observed in 50% of participants. The mean age of participants with metabolic syndrome was 58.22 ± 11.16 years, and without MetS was 53.02 ± 13.52 years. Fasting blood sugar, uric acid and serum xanthine oxidase were identified with 172.21 ± 87.42, 7.58 ± 0.74 and 2.99 ± 0.91 in participants with the metabolic syndrome. High-density lipoproteins were <50 mg/dl in the majority of female participants with metabolic syndrome. Similarly, it was <40 in the majority of male patients with metabolic syndrome. All the female participants with MetS had Waist Circumference ≥ 80. Whereas, all the male participants with MetS had Waist Circumference ≥ 90. The Uric Acid was ≥ 7.35 for 70.31% participants with metabolic syndrome. Whereas, the Serum xanthine oxidase was ≥ 1.95 for 88.71% of participants. The uric acid had sensitivity, specificity, false positive rate, false-

negative rate, positive predictive value, negative predictive value and total diagnostic accuracy of 70.31%, 76.56%, 23.44%, 29.69%, 75%, 72.06% and 73.44% in predicting the presence of the metabolic syndrome. The serum xanthine oxidase had sensitivity, specificity, false positive rate, false-negative rate, positive predictive value, negative predictive value and total diagnostic accuracy of 88.71%, 90.63%, 9.38%, 11.29%, 90.16%, 89.23% and 89.68% in predicting the presence of the metabolic syndrome.

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ANNEXURES

INFORMED CONSENT FORM

STUDY TITLE: "ROLE OF XANTHINE OXIDASE AND URIC ACID IN METABOLIC SYNDROME"

STUDY NUMBER:

SUBJECT'S NAME: **HOSPITAL NUMBER:**

AGE:

It is hoped that the knowledge of relevant study might be useful for early identification of patients at high risk requiring prior intervention. If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. This information collected will be used for only dissertation and publication. The institutional ethical committee has reviewed this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understood the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for dissertation and publication only.

Signature or thumb impression of the subject: Date:

Name and signature of the witness: Date:

Name and signature of person obtaining consent Date:

ಮಾಹಿತಿಯುಕ್ತ ಸಮ್ಮತಿಯ ನಮೂನೆ

ಇದು ಸೂಕ್ತ ಪೂರ್ವಸೂಚಕ ಅಂಶಗಳಲ್ಲಿ ಜ್ಞಾನ ತೀವ್ರ ನಿಗಾ ಚಿಕಿತ್ಸೆಯ ಅಗತ್ಯ ಹೆಚ್ಚಿನ ಅಪಾಯ ರೋಗಿಗಳ ಆರಂಭಿಕ ಗುರುತಿನ ಉಪಯುಕ್ತ ಇರಬಹುದು ಭರವಸೆಯಿದೆ . ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪುತ್ತೀರಿ ವೇಳೆ ನೀವು ಅಥವಾ ನೀವು ಅಥವಾ ಎರಡೂ ಜವಾಬ್ದಾರಿ ವ್ಯಕ್ತಿಯಿಂದ ಮಾಹಿತಿ (ಪ್ರತಿ proforma ಮಾಹಿತಿ) ಸಂಗ್ರಹಿಸುತ್ತದೆ . ನಿಮ್ಮ ಆಸ್ಪತ್ರೆ ದಾಖಲೆಯಿಂದ ಚಿಕಿತ್ಸೆ ಮತ್ತು ಸೂಕ್ತ ವಿವರಗಳನ್ನು ಸಂಗ್ರಹಿಸುತ್ತದೆ . ಸಂಗ್ರಹಿಸಿದ ಈ ಮಾಹಿತಿ ಮಾತ್ರ ಪ್ರೌಢಪ್ರಬಂಧದಲ್ಲಿ ಮತ್ತು ಪ್ರಕಟಣೆ ಬಳಸಲಾಗುತ್ತದೆ . ಈ ಅಧ್ಯಯನವು ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿಯು ವಿಮರ್ಶಿಸುತ್ತದೆ ಮಾಡಲಾಗಿದೆ . ನೀವು ಭಾಗವಹಿಸಲು ಇಚ್ಛಿಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುತ್ತಾನೆ ಆರೈಕೆ ಬದಲಾಗುವುದಿಲ್ಲ . ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಕೊಂಡಲ್ಲಿ ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು ಸೈನ್ / ಒದಗಿಸುವ ಅಗತ್ಯವಿದೆ .

ನಾನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನದಿಂದ ಹಿಂತೆಗೆದುಕೊಳ್ಳುವಂತೆ ಮತ್ತು ಈ ನನ್ನ ಮುಂದಿನ ಆರೈಕೆ ಬದಲಾಗುವುದಿಲ್ಲ ಉಚಿತ ಉಳಿಯಲು ಎಂದು ಅರ್ಥ . ನಾನು ಓದಲು ಅಥವಾ ನನಗೆ ಓದಲು ಮಾಡಲಾಗಿದೆ ಮತ್ತು ಅಧ್ಯಯನದ ಉದ್ದೇಶ , ಬಳಸಲಾಗುವ ವಿಧಾನ , ಅಧ್ಯಯನ ಮತ್ತು ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಸಂಗ್ರಹಿಸಿದ ಮತ್ತು ಬಹಿರಂಗ ನಡೆಯಲಿದೆ ಮಾಹಿತಿಯನ್ನು ಪ್ರಕೃತಿಯಲ್ಲಿ ನನ್ನ ಒಳಗೊಳ್ಳುವಿಕೆ ಸಂಬಂಧಿಸಿದ ಅಪಾಯ ಮತ್ತು ಲಾಭಗಳನ್ನು ಅರ್ಥ . ನಾನು ಅಧ್ಯಯನ ಮತ್ತು ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ವಿವಿಧ ಅಂಶಗಳನ್ನು ನನ್ನ ತೃಪ್ತಿ ಉತ್ತರಿಸುವ ಬಗ್ಗೆ ನನ್ನ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ಅವಕಾಶ ಹೊಂದಿದ್ದರು . ನಾನು , ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಮತ್ತು ಪ್ರೌಢಪ್ರಬಂಧದಲ್ಲಿ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹಣೆ ಮತ್ತು ಡಿಸ್ಕ್ಲೋಸರ್ ಅಧಿಕೃತಗೊಳಿಸಲು ಒಪ್ಪುತ್ತೀರಿ ರುಜುಮಾಡಿರುವ .

ವಿಷಯದ ಹೆಸರು

(ಪಾಲಕರು / ಗಾರ್ಡಿಯನ್ಸ್ ಹೆಸರು)

DATE : ಸಹಿ / ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು

ಒಪ್ಪಿಗೆ ತೆಗೆದುಕೊಳ್ಳುವ ವ್ಯಕ್ತಿಯ ಹೆಸರು ಮತ್ತು ಸಹಿ

PROFORMA FOR DATA COLLECTION

NAME: IP NO:
AGE:

SEX:

ADDRESS:

OCCUPATION:

DETAILED HISTORY:

ANTHROPOMETRIC MEASUREMENT:

HEIGHT:

WEIGHT:

BODY MASS INDEX:

WAIST CIRCUMFERENCE:

GENERAL PHYSICAL EXAMINATION:

PULSE:

BLOOD PRESSURE:

SYSTEMIC EXAMINATION:

CARDIOVASCULAR EXAMINATION:

RESPIRATORY EXAMINATION:

PER ABDOMINAL EXAMINATION:

CENTRAL NERVOUS SYSTEM EXAMINATION:

LABORATORY DATA:

1. FASTING PLASMA GLUCOSE:

2. FASTING LIPID PROFILE:

3. RENAL FUNCTION TESTS:

4. SERUM URIC ACID LEVEL:

5. XANTHINE OXIDASE LEVEL:

OTHER TESTS:

USG ABDOMEN

PATIENT INFORMATION SHEET

Study Title: ROLE OF XANTHINE OXIDASE AND URIC ACID IN METABOLIC SYNDROME

Principal investigator: Dr CHARCHIT MEHTA

Study site : R.L Jalappa Hospital and Research Center attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Purpose of the study: This study is aimed to evaluate serum level of uric acid and xanthine oxidase in metabolic syndrome and their role as early marker in metabolic syndrome.

Voluntary Participation: Your participation in this study is entirely voluntary. There is no compulsion to participate in this study. You will be no way affected if you do not wish to participate in the study. You are required to sign only if you voluntarily agree to participate in this study. Further you are at a liberty to withdraw from the study at any time. We assure you that your withdrawal will not affect your treatment by the concerned physician in any way.

Procedure : If you fulfil our inclusion criteria , we will take 5ml of venous blood from your arm and test FBS, RFT, Xanthine Oxidase, Uric Acid and lipid profile the cost will be borne by researcher.

Confidentiality: All information collected from you will be strictly confidential & will not be disclosed to anyone except if it is required by the law. This information collected will be used only for research. This information will not reveal your identity.

We would not compel you any time during this process; also we would greatly appreciate your cooperation to the study. We would like to get your consent to participate in the study.

For any information you are free to contact investigator. This study has been approved by the Institutional Ethics Committee & has been started only after their formal approval. The sample collected will be stored in the institute and I request you to permit us to store and use this sample for any future study.

MASTER SHEET

Sno	UHID	Age	Gender	Type 2 DM	FBS (100mg/dl)	HDL (mg/dl)	TG (mg/dl)	Waist Circumference	HTN	Metabolic Syndrome	Uric Acid (mg/dl)	Serum xanthine oxidase (U /mg)	Uric_acid_2	serum_2	HDL for male	HDL for females	Waist circumference females	Waist circumference for males
1	668638	70	m	1	132.00	35.00	123.00	94	1	1	7.50	3.70	2	2	1			2
2	668166	43	m	1	119	61	130	98	2	2	7.10	1.90	1	1	2			2
3	668752	45	m	2	82	62	130	83	2	2	7.60	1.60	2	1	2			1
4	666198	60	m	1	182	36	160	108	1	1	7.30	4.90	1	2	1			2
5	668730	64	m	2	69	48	129	89	2	2	7	1	1	1	2			1
6	668220	58	m	2	98	38	265	88	2	1	7.90	3.60	2	2	1			1
7	668235	60	m	2	82	36	200	90	1	1	8.80	2.90	2	2	1			2
8	664790	60	m	1	109	29	219	92	2	1	8	1.10	2	1	1			2
9	669026	60	m	2	67	51	170	95	2	2	7.20	2.10	1	2	2			2
10	669190	65	m	1	111	34	139	92	1	1	7.90	5.10	2	2	1			2
11	854592	60	m	2	88	48	130	94	1	2	7.20	0.70	1	1	2			2
12	669076	56	m	1	157	33	172	104	1	1	7.60	3.30	2	2	1			2
13	669428	45	m	2	84	41	145	87	1	2	6.40	1.70	1	1	2			1
14	669450	49	m	2	92	44	207	90	2	2	6.50	0.60	1	1	2			2
15	661587	46	m	1	104	35	208	94	2	1	6.90	1.70	1	1	1			2
16	667707	52	m	2	91	29	228	92	2	1	7.60	5.10	2	2	1			2
17	844043	60	m	2	69	41	290	95	2	2	7.90	1.90	2	1	2			2
18	669501	40	m	1	124	51	170	93	2	1	7.40	2.50	2	2	2			2
19	669706	29	m	2	87	53	128	90	1	2	6.20	1.10	1	1	2			2
20	613746	42	m	2	99	34	102	98	1	1	7.60		2		1			2
21	678640	48	m	1	109	41	209	88	1	2	8.10	0.80	2	1	2			1
22	678736	55	m	1	116	39	188	98	1	1	5.90	2.30	1	2	1			2
23	678900	67	m	2	87	33	130	93	1	1	6.90	2.80	1	2	1			2
24	619038	46	m	2	82	52	80	62	2	2	6.20	2.10	1	2	2			1
25	678446	78	m	1	218	22	300	90	2	1	6.10	1.90	1	1	1			2
26	677215	51	m	1	321	29	290	105	1	1	7.50	3.20	2	2	1			2
27	669970	72	m	2	97	46	240	94	2	2	7.10	1.40	1	1	2			2
28	677659	74	m	2	109	52	120	92	2	2	7.10	1	1	1	2			2
29	679056	55	m	1	364	21	404	97	2	1	7.80	3.90	2	2	1			2
30	678908	55	m	1	404	29	332	96	1	1	7.60	5	2	2	1			2

31	592980	60	m	1	229	37	225	92	1	1	8.10	2.40	2	2	1			2
32	676198	58	m	2	77	44	142	94	1	2	7	2.10	1	2	2			2
33	639755	45	m	2	77	46	190	83	2	2	7.70	0.90	2	1	2			1
34	625169	80	m	1	219	33	188	102	2	1	7.60	4.10	2	2	1			2
35	678531	65	m	1	119	47	154	94	2	1	7.40	1.50	2	1	2			2
36	679082	55	m	1	143	39	153	99	1	1	7.60	2.30	2	2	1			2
37	679296	58	m	2	84	60	115	90	1	2	6	1.60	1	1	2			2
38	679486	63	m	2	82	54	110	92	1	2	7.50	1.90	2	1	2			2
39	676433	79	m	1	174	38	138	93	2	1	7.90	3	2	2	1			2
40	679433	33	m	2	69	55	160	78	2	2	7.10	1.10	1	1	2			1
41	678543	65	m	2	98	53	188	113	2	2	7.30	0.70	1	1	2			2
42	678966	73	m	1	214	33	144	94	1	1	7.90	2	2	2	1			2
43	678746	75	m	2	87	58	160	110	2	2	7.40	0.50	2	1	2			2
44	678224	55	m	2	84	55	241	88	2	2	7	1.80	1	1	2			1
45	669862	59	m	2	88	44	223	89	1	2	7	1	1	1	2			1
46	669861	57	m	1	167	33	99	94	2	1	7.60	2	2	2	1			2
47	669828	67	m	1	159	33	213	90	2	1	7.30	2.60	1	2	1			2
48	669718	36	m	2	87	59	214	99	2	2	7.70	1.20	2	1	2			2
49	669734	62	m	2	82	57	200	98	2	2	6.20	0.60	1	1	2			2
50	669483	74	m	1	143	52	188	96	1	1	6.40	3.90	1	2	2			2
51	654867	68	m	2	77	60	156	84	2	2	6.20	0.40	1	1	2			1
52	669423	38	m	1	156	42	170	97	2	1	8.20	3.20	2	2	2			2
53	669390	66	m	2	97	53	210	95	2	2	6.90	0.50	1	1	2			2
54	614302	45	m	1	108	27	220	96	2	1	7.80	3.10	2	2	1			2
55	670158	56	m	1	249	29	129	94	2	1	6.20	3.30	1	2	1			2
56	670164	45	m	2	91	56	137	91	1	2	7.40	0.70	2	1	2			2
57	670079	58	m	2	83	58	130	79	1	2	7.20	0.50	1	1	2			1
58	668689	46	m	1	222	37	170	89	1	1	7.10		1		1			1
59	670195	45	m	2	82	57	100	88	1	2	6.20	0.70	1	1	2			1
60	670121	75	m	1	124	52	99	93	1	1	7.70	2.80	2	2	2			2
61	669709	35	m	2	68	55	83	76	1	2	6.90	0.60	1	1	2			1
62	668159	45	m	2	87	37	201	79	2	1	7.60	3.40	2	2	1			1
63	670504	84	m	2	69	58	132	69	2	2	7.60	2.20	2	2	2			1
64	670153	78	m	2	88	33	187	112	1	1	8	4.20	2	2	1			2
65	670646	55	m	2	72	56	173	85	1	2	7	0.40	1	1	2			1
66	670479	59	m	2	89	51	129	84	2	2	6.30	0.70	1	1	2			1

67	609619	51	m	1	162	52	139	87	1	2	7	0.80	1	1	2			1
68	669725	54	m	1	119	54	174	89	2	2	6.90	0.90	1	1	2			1
69	669738	35	m	2	68	59	134	76	2	2	6.50	0.80	1	1	2			1
70	649097	62	m	1	298	37	324	108	1	1	8.30	4.10	2	2	1			2
71	670694	54	m	1	432	52	152	89	2	2	7.10	1.90	1	1	2			1
72	414402	58	m	1	337	40	182	98	2	1	7.10	2.10	1	2	2			2
73	670687		m	2	87	38	127	93	2	2	6.70	0.60	1	1	1			2
74	670579	44	m	1	126	44	147	92	1	1	7.30	3.50	1	2	2			2
75	670612	36	m	2	91	41	138	82	1	2	7.50	0.80	2	1	2			1
76	670681	50	m	2	97	38	190	93	1	1	8.20	2.60	2	2	1			2
77	630735	56	m	1	231	38	358	100	1	1	8.80	3.10	2	2	1			2
78	671330	35	m	2	87	56	122	86	2	2	6.60	0.70	1	1	2			1
79	671554	75	m	1	227	62	150	83	2	2	6.40	0.80	1	1	2			1
80	803073	48	f	1	128	47	180	88	1	1	7.80	3.20	2	2		1	2	
81	671726	50	f	2	79	58	203	90	2	2	5.20	1.50	1	1		2	2	
82	671585	60	f	2	88	59	147	76	2	2	7	1.20	1	1		2	1	
83	718760	66	f	1	147	43	102	96	1	1	6.80	4.10	1	2		1	2	
84	671953	48	f	2	73	54	194	85	1	2	6.60	2.30	1	2		2	2	
85	671517	49	f	1	167	50	188	84	2	1	7.90	1.30	2	1		2	2	
86	671167	65	f	1	132	60	197	78	2	2	6.40	0.90	1	1		2	1	
87	671947	45	f	1	99	44	250	100	2	1	8.20	2.70	2	2		1	2	
88	670726	65	f	2	84	59	147	90	1	2	8.10	2.60	2	2		2	2	
89	671876	65	f	1	103	41	170	80	2	1	7.50	3.50	2	2		1	2	
90	670991	65	f	2	90	46	157	78	1	2	7.50	1.50	2	1		1	1	
91	625948	56	f	2	110	48	201	84	2	1	5.90	4	1	2		1	2	
92	671460	26	f	2	72	46	168	84	1	1	7.50	1.80	2	1		1	2	
93	672045	53	f	1	133	46	90	81	1	1	9.60	2.40	2	2		1	2	
94	671903	48	f	2	62	49	199	77	1	2	7.20	1	1	1		1	1	
95	672267	43	f	2	88	55	204	84	2	2	7	0.60	1	1		2	2	
96	672406	65	f	1	117	34	321	79	1	2	7.40	1.20	2	1		1	1	
97	672373	65	f	2	84	40	214	82	1	1	8.20	2.40	2	2		1	2	
98	870291	65	f	2	73	59	168	88	2	2	7.90	0.70	2	1		2	2	
99	870293	60	f	1	183	38	183	89	1	1	7.50	2.30	2	2		1	2	
100	869919	21	f	2	92	55	173	81	2	2	6.20	0.80	1	1		2	2	
101	867375	51	f	1	101	51	180	83	1	1	5.90	2.70	1	2		2	2	
102	868952	65	f	2	91	45	160	84	1	1	7.10	3.60	1	2		1	2	
103	870260	55	f	1	222	20	312	116	2	1	7.80	3	2	2		1	2	

104	870293	65	f	1	298	21	233	113	1	1	9.20	1.10	2	1		1	2	
105	870323	60	f	1	122	40	98	101	2	1	6.80	2.40	1	2		1	2	
106	869999	60	f	2	89	52	100	105	2	2	7.30	0.70	1	1		2	2	
107	866270	70	f	1	357	31	334	95	1	1	7.60	3.20	2	2		1	2	
108	866297	80	f	1	357	41	145	103	1	1	7.40	2.60	2	2		1	2	
109	869432	63	f	1	9999	34	122	90	1	1	6.90	2.30	1	2		1	2	
110	870254	65	f	2	84	46	109	90	2	2	6.20	0.70	1	1		1	2	
111	870298	65	f	2	92	40	221	77	1	2	6.60	0.40	1	1		1	1	
112	870296	65	f	2	75	52	188	83	2	2	6.50	0.90	1	1		2	2	
113	869974	48	f	2	76	47	144	90	2	2	7.50	0.80	2	1		1	2	
114	869958	55	f	2	97	39	156	96	2	1	7.30	3.40	1	2		1	2	
115	870315	50	f	1	166	44	210	92	2	1	8.80	3.10	2	2		1	2	
116	870293	52	f	2	75	44	150	78	2	2	6.70	0.60	1	1		1	1	
117	870312	41	f	2	83	50	138	66	2	2	6.50	0.70	1	1		2	1	
118	870097	65	f	1	224	42	235	103	2	1	8.20	2.60	2	2		1	2	
119	870132	28	f	2	68	32	118	78	2	2	6.20	0.90	1	1		1	1	
120	870219	59	f	2	86	46	151	86	1	1	7.80	2.80	2	2		1	2	
121	870169	44	f	1	356	40	422	121	1	1	8.60	3.40	2	2		1	2	
122	859446	23	f	2	74	39	135	76	2	2	6.50	0.90	1	1		1	1	
123	870087	68	f	1	165	41	241	119	2	1	7.90	3.40	2	2		1	2	
124	870246	62	f	1	328	44	190	97	1	1	7	2.90	1	2		1	2	
125	870297	48	f	1	164	34	247	108	2	1	7.60	2.90	2	2		1	2	
126	870255	56	f	1	152	60	120	78	2	2	6.70	0.90	1	1		2	1	
127	870275	45	f	2	98	52	160	79	2	2	6.20	1.10	1	1		2	1	
128	870229	38	f	2	88	63	119	74	2	2	6.20	0.60	1	1		2	1	

KEY OF THE MASTER SHEET:

VARIABLE	KEY OF THE VARIABLE
Type 2 DM, HTN, Metabolic Syndrome	1 =Yes, 2 =No
Uric_acid_2	1 = <7.35, 2 = ≥7.35, (units – mg/dl)
Serum_2	1 = <1.95, 2 = ≥1.95, (units – U/mg)
HDL for males	1 = <40, 2 = ≥40, (units – mg/dl)
HDL for females	1 = <50, 2 = ≥50, (units – mg/dl)
Waist circumference for males	1 = <90, 2 = ≥90, (units – cm)
Waist circumference for females	1 = <80, 2 = ≥80, (units – cm)