PREVALENCE OF HYPERURICEMIA AND ITS ASSOCIATION WITH METABOLIC SYNDROME IN TYPE 2 DIABETES MELLITUS PATIENTS IN HAWASSA COMPREHENSIVE SPECIALIZED HOSPITAL

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Abstract

Background: - Type 2 Diabetes mellitus (T2DM) is associated with cardiovascular complications, of which metabolic syndrome (Mets) plays a prominent role. The metabolic syndrome is a cluster of cardiovascular risk factors that is characterized by central obesity, insulin resistance, dyslipidemia and hypertension. Hyperuricemia is a condition in which the subject has increased serum uric acid levels. Studies have noted that an elevated level of uric acid predicts the development of diabetes, obesity, hypertension and metabolic syndrome.

Methods: - Institution based cross sectional study was conducted in Hawassa Comprehensive Specialized Hospital medicine department from February to June 2017. A diabetes mellitus patient who visited the hospital during the study period and fulfilled the inclusion criteria was selected by using simple random sampling technique. A total of 314 subjects were included in the study. The data was collected by nurses who had previous data collection experience using standardized quastionnaeries. About 5 milliliters (ml) of venous blood sample was drawn from each study participant after overnight fasting. The collected data was entered in to Epidata and analyzed by using SPSS version 20 software. Bivariate and Multivariate Logistic Regression analysis (if $p>0.2$ for Bivariate) was used to determine the association between explanatory variables and the outcome variable. Statistical significance was declared at P value<0.05.

Result: - The prevalence of hyperuricemia among the study participants was 33.8% and the prevalence of metabolic syndrome was 70.1%. Hyperuricemia was significantly associated with Metabolic syndrome ($P=0.004$).Hyperuricemia was strongly correlated with Triglycerides ($P<0.001$), Diastolic blood pressure ($p=0.006$), systolic blood pressure ($p<0.0001$), and Waist circumference ($p<0.0001$).

Conclusion:-The prevalence of hyperuricemia and metabolic syndrome among T2DM was high and hyperuricemia was associated with metabolic syndrome. Hyperuricemia also correlated with some of the components of metabolic syndrome.

Recommendation: T2DM better be checked for their uric acid level and further research should be conducted with better study design.

Key words: - Hyperuricemia, T2DM, Metabolic syndrome, Hawassa, Ethiopia

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List of abbreviations

BMI-Body Mass Index

BP-blood pressure,

CI- confidence interval

DBP- Diastolic blood pressure;

DM-Diabetes Mellitus

FPG-Fasting plasma Glucose

HDL-C-high density lipoprotein cholesterol;

IDF-International Diabetic Federation

IR-Insulin Resistance

LDL-C-Low density lipoprotein cholesterol;

MetS-Metabolic Syndrome

SBP- Systolic blood pressure;

SD-Standard deviation

SUA-Serum Uric Acid

TG- Triglycerides;

T2DM-Type 2 Diabetic Mellitus

UA-Uric Acid

WC-Waist Circumference

CHAPTER ONE: INTRODUCTION

1.1. Background

Hyperuricemia is a condition in which the subject has increased serum uric acid levels. Studies have noted that an elevated level of uric acid predicts the development of diabetes, obesity, hypertension and the metabolic syndrome (1-3). It also plays a role in the development of renal and metabolic diseases. Serum uric acid is a final enzymatic product of purine metabolism in humans, and it is suggested that hyperuricemia is associated with metabolic syndrome, and they may have common pathophysiology (1, 4). The metabolic syndrome is a cluster of cardiovascular risk factors that is characterized by central obesity, insulin resistance, dyslipidemia and hypertension (5-7). The principal underlying pathophysiologic abnormality is insulin resistance (IR), which is mainly associated with abdominal obesity. IR eventually results in dyslipidemia, hypertension, impaired carbohydrate metabolism, and other metabolic abnormalities. (8).

A recent 15-year follow up study demonstrated that those with hyperuricemia have 1.36 times the risk of developing insulin resistance than normouricemia (9). Furthermore, a study on mice demonstrated that lowering uric acid in obese mice can reduce insulin resistance. (10). All the data suggest that hyperuricemia can be detected prior to the development of hyperinsulinemia.

Diabetic patients who continue to be hyperuricemic appear to be at increased risk of developing diabetic complications, especially renal disease(11)via intra renal crystal deposition(12).

Evidence showed that the patients with both gout and type 2 Diabetes exhibited a mutual inter-dependent effect on higher incidences. Furthermore, obese patients often demonstrated insulin resistance and adipose tissue macrophage with low-grade inflammation, which is suggested to be the major contributor. Although alcohol intake is considered a risk for developing hyperuricemia, moderate alcohol intake showed a lower risk for developing type two diabetes and insulin resistance. Hyperinsulinemia reduces renal excretion of uric acid on the proximal tubular of the kidney leading to hyperuricemia, which has deleterious effects on endothelial function and on nitric oxide bioavailability, thus causing hyperinsulinemia(13).Uric acid may promote insulin

resistance by inhibiting endothelial function by inducing anti proliferative effects on endothelium and impairing nitric oxide production and inflammation(14).

Type 2 diabetes mellitus (type 2 DM) is associated with cardiovascular complications, of which metabolic syndrome (Mets) plays a prominent role (1, 15, 16). Serum Uric Acid is as independent risk factor for development and progression of Coronary Artery Disease.

Since metabolic syndrome is a cluster of various risk factors like obesity, hypertension, hyperglycemia, dyslipidemia for the development of atherosclerotic disease, hyperuricemia can also be included as one of the components of metabolic syndrome (17).

The prevalence of obesity, hypertension, diabetes, dyslipidemia, and hyperuricemia has been increasing over the last few decades due to rising living standards occurring with modernization and urbanization. Some reports on SUA and the metabolic syndrome have noted that increased SUA concentration is associated with an increased prevalence of some of the parameters - obesity, dyslipidemia and hypertension –of the metabolic syndrome. In these reports carried out in non-DM subjects the documented prevalence rates of hyperuricemia ranged from 13-19% with greater proportions of males having elevated levels of Serum Uric Acid compared to females(4, 16, 18).

Hyperuricemia also predicts stroke in diabetic and non diabetic subjects and predicts the development of hypertension and renal disease in the general population.SUA levels are often increased in subjects with MetS. However, none of the proposed sets of diagnostic criteria includes SUA levels in the definition of MetS. (5, 19).

Since hyperuricemia was first described as being associated with hyperglycemia and hypertension, there has been a growing interest in the association between elevated Uric Acid and other metabolic abnormalities of hyperglycemia, abdominal obesity, dyslipidemia, and hypertension, as well as a continuing debating on hyperuricemia as an additional component of the metabolic syndrome.

1.2. Statement of the problem

The total worldwide burden of hyperuricemia among DM patients is not well known. However, there exist different studies in different part of the world. A metaanalysis of cohort studies reported an overall 17% increased diabetes risk per mg/dL uric acid increase (20). In analysis limited to studies that corrected for at least three metabolic confounders such as BMI, the association attenuated to 11%, but remained significant, this suggests an independent association of hyperuricemia with diabetes mellitus(21).

Another study showed that the prevalence of metabolic syndrome, central obesity, hypertension, high triglycerides (TGs), CKD, and macro albuminuria was significantly higher in patients with hyperuricemia than those in the lowest tertile of SUA (T1). One standard deviation (SD) increment of SUA was significantly associated with metabolic syndrome, central obesity, and high TGs after adjustment for age, sex, estimated glomerular filtration rate (eGFR), and albuminuria. The odds of CKD went up to 1.37-fold with every 1 SD increment of SUA, independent of age, sex, and components of metabolic syndrome. There was a significant, graded increase in odds of CKD by increasing SUA levels and the number of metabolic syndrome risk factor.(22).Another study also found almost identical directions and magnitudes of associations, with a 20% increased diabetes risk per 59.5 mmol/L uric acid increase in an obesity-adjusted model, which attenuated to 13% after further adjustment for metabolic risk Factors. Still, there is limited number of studies done in Africa on prevalence of hyperuricemia and its association in DM patients, apart only one study indicating the prevalence to be 25.3% (1).

Available data suggests that hyperuricemia may not be benign, and appears to be a potential contributor to the worldwide obesity pandemic, diabetes, kidney and cardiovascular disease states. **I**dentifying risk factors for the development of type 2 diabetes is essential for its early screening and prevention. Serum uric acid (SUA) level has been suggested to be associated with risk of type 2 diabetes. Some reports on SUA and metabolic syndrome have noted that increased SUA concentration is associated with increased prevalence of some of the parameters of the metabolic syndrome like obesity, dyslipidemia and hypertension(1-3).

The possible role of elevated SUA in the MetS is a subject that has become topical in the past few years with some studies reporting SUA to be related to the presence of the Mets(23) .

Available reports on hyperuricemia from sub-Saharan Africa also showed that hyperuricemia was found to be associated with increased cardio-metabolic risk such as obesity, dyslipidemia, hyperglycemia and hypertension. Pathologically and epidemiologically, it has been indicated that elevated SUA concentration is correlated with lifestyle factors (high alcohol intake in particular) and various metabolic profiles (especially high values of BMI, blood pressure, fasting plasma glucose and triglycerides, and low HDL cholesterol values (24).

Elsewhere, another report showed that Serum uric acid had independent association with MetS components, and increases the risk of MetS by near two folds(25). An increased prevalence of nephrolithiasis has been reported in patients with diabetes. Because insulin resistance, characteristic of the Bio-markers for metabolic syndrome and T2DM, results in lower urine pH through impaired kidney ammoniagenesis and because a low urine pH is the main factor of uric acid (UA) stone formation, it was hypothesized that T2DM should favor the formation of UA stones(26). More importantly, hyperuricemia can be treated and metabolic syndrome can be reversed so that cardiovascular disease and T2DM can be prevented.

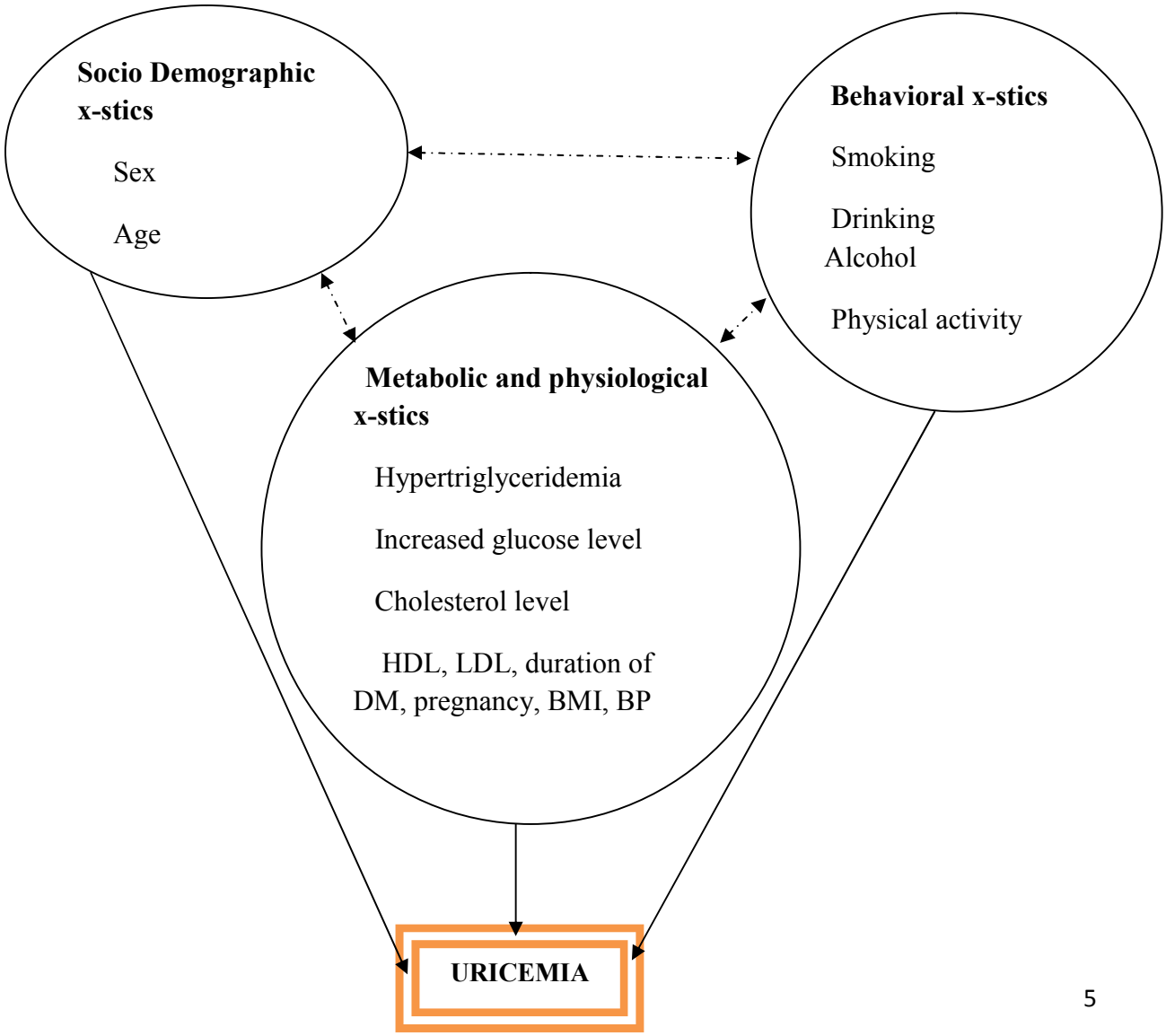
Diabetic patients who continued to be hyperuricemic appeared to be at increased risk of developing diabetic complications. Hyperuricemia is significantly associated with DM and can significantly increase morbidity and mortality from diabetes if not managed in time.

Hyperuricemia has been attributed to hyperinsulinemia in metabolic syndrome and to decreased uric acid excretion in kidney dysfunction, but it is not acknowledged as a main mediator of metabolic syndrome, renal disease, and cardiovascular disorder development. Hyperuricemia and its complication have been always overseen and it could be a challenge for prognosis of DM patients. Even though there are different studies, they have Contradicted idea about the level of hyperuricemia among DM patient. None of the proposed sets of diagnostic criteria for MetS included SUA levels in the definition of MetS. Though chronic diseases such as hypertension and DM is gaining global concern this day, the concern given to it in Africa is very less. Research done concerning DM patients that focused on hyperuricemia specifically in Ethiopia until recently is very less. Although there are some activities going on concerning DM patients, the attention given from government was little. Specifically we couldn't find a research done concerning the relationship between hyperuricemia and metabolic syndrome in DM patients in

Ethiopia until this research was conducted. Thus, we hope to document the scope of hyperuricemia and describe the association of hyperuricemia and metabolic syndrome in T2DM patients attending in outpatient department of hawassa university comprehensive specialized hospital. Moreover, we hope to determine the prevalence of hyperuricemia in T2DM, determine the correlation between hyperuricemia and MetS components in T2DM.

1.3. Conceptual frame work

The different variables that are assessed in this study were categorized into socio demographic, behavioral, and metabolic and physiological components. In addition the interaction between the independent variables which is not addressed by this study was indicated by a broken line. The solid lines indicate the association between the components of the independent factors and the dependent variable that the study attempts to assess.



1.4. Significance of the study

This study was conducted to determine the magnitude of hyperuricemia and its association with MetS in T2DM patients at HUSCH. It is possible to say that the increased cardiovascular disease risk is associated with the MetS is partially attributed to elevated circulating SUA concentration. Hyperuricemia and its complication have been always overseen and it could be a challenge for prognosis of T2DM patients.

Even though some studies have been carried out on prevalence of MetS among T2DM patients, the prevalence of hyperuricemia and its association with MetS among T2DM is scanty from the southern region of the country particularly in the study area. The outcome of this study will help to generate information about hyperuricemia and its possible relationship with MetS among T2DM patients.

In addition, determining the prevalence of hyperuricemia at early stage will have paramount significance in reducing progression and complication of disease. On the other hand, it can be a good indicator of general hyperuricemia prevalence in T2DM patients at the study area. Such data are fundamental for health planers and caregivers for evidence-based intervention and guide future policy makers. This study may also have its own contribution in making push NCEP and other organizations for inclusion of serum uric acid level as a new marker for MetS and making Serum uric acid level as one set of diagnostic criteria in the definition of MetS.

CHAPTER TWO: LITERATURE REVIEW

Hyperuricemia has recently gained attention as it is not only plays an important role in the development of metabolic diseases but it is also a cardiovascular risk factor. The serum uric acid level being higher in pre-diabetes than controls and lower in diabetes mellitus than pre-diabetes may serve as a potential inexpensive biomarker of deterioration of glucose metabolism(27).

A case–control study comprised of 101 non-smoking individuals (41 in the MetS group and 60 in the non-MetS group) showed that serum uric acid was significantly higher in MetS group than non-MetS group (5.70 ± 1.62 vs 4.97 ± 1.30 mg/dL, respectively, P = 0.001) and uric acid was positively correlated with triglycerides, and negatively with HDL-C. This study also showed that for every 1 mg/dl elevation in the SUA level, the risk of MetS approximately is increased by 2-folds (OR: 2.11, 95 % CI: 1.30-3.41) (25).

A study of 688 type 2 DM patients, done in Seoul Korea, MetS prevalence was 46.9 % for males, and 65.1% for females. Patients with T2DM and MetS showed significantly higher insulin resistance than T2DM without MetS, confirming that insulin resistance is an important feature of MetS in T2DM patients. Patients with T2DM and MetS showed higher BMI, waist circumference, blood triglycerides, atherogenic index, C-reactive protein and lower HDL cholesterol. In recent years, concerns with regard to the association of diet with MetS have grown. In our study with non-DM elderly people, higher % energy from carbohydrate, and lower intakes of antioxidant vitamins were considered to be associated with the risk of MetS. Patients with T2DM and MetS showed significant positive correlations between intakes of energy, carbohydrate, protein and lipids with BMI, weight, as well as waist circumference. These associations were not found in patients with T2DM without MetS. Nutritional risk factors for MetS among middle-aged T2DM subjects would be excessive carbohydrate intake with low intakes of fat, protein, vitamins, and minerals (28).

Another cross sectional study conducted on Taiwan adults with health indicated positive association between hyperuricemia and metabolic syndrome and between hyperuricemia and each component of metabolic syndrome was observed(21). Regarding the significance of smoking, a study in Japan, Tokyo, revealed that the contribution of current smoking is not significant and moderate physical activity is inversely associated with the number of MetS (29).

An observational longitudinal study carried out on T2DM patients in Maharashtra, India, showed that out of the study subject 45.3% of them was diagnosed with metabolic syndrome with higher prevalence in male (53.4%) than females (33.9%).Hyperuricemia was found in 25.3% with higher prevalence in males (33%) than females (14.5%). Hyperuricemia and metabolic syndrome was found in 21.3% patients with higher prevalence among males 27.3% than females 12.9 %.(1). This study also showed that patients with hyperuricemia and metabolic syndrome, compared to those without hyperuricemia and metabolic syndrome respectively, had higher mean FBS (139.31 versus 117.23), mean duration of diabetes (12.66 versus 5.64), mean BMI (28.71 versus 24.61), systolic BP (128.50 versus 122.12), diastolic BP (80.63 versus 74.27), TG (176.28 versus 141.69) and lower HDL (39.63 versus 52.03)(1).

Another cross sectional study carried out at Outpatients Medicine Department of Dr. Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation, Chinna Avutapalli showed that the circulatory levels of glucose, total cholesterol and triglycerides were found to be elevated in the diabetics of either sex as compared to those in the controls. In addition, there was no significant difference in the serum uric acid levels between the diabetics and the non-diabetics, either in males or in females, which is in contrary to some of the above study mentioned. The same study showed a negative correlation between the fasting plasma glucose and the serum uric acid levels in both male [$r = -0.60$] and female [$r = -0.60$] among the study participants. The serum uric acid levels marginally decreased with an increased duration of diabetes and there was a significantly decreased ($P < 0.05$) serum uric acid level in female diabetics as compared to the corresponding non-hypertensive diabetics. In conclusion, there was a significant decrease in the serum uric acid levels in hypertensive diabetics (in both males and females) in comparison with the non-hypertensive diabetics(23).

A cross sectional study in Geriatrics Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt, 200 hospitalized elderly patients were analyzed and the results were as follows: the prevalence of hyperuricemia was 21.0% in elderly men and 15.1% in elderly women. Multivariate logistic regression analysis revealed that BMI ≥ 30 ($p = 0.031$, OR = 1.1), hypertension ($p = 0.019$, OR = 1.8), high triglycerides level ($p = 0.018$, OR = 2.9) and hyperuricemia ($p = 0.023$, OR= 3.7) were independently associated with MetS (30).

A case control study in Lucknow, Uttar Pradesh, India showed that SUA, glycosylated hemoglobin, and low-density lipoprotein of male and female cases of T2DM with Hypertension(HTN), compared to control, were ($p<0.05$) highly significant and also serum triglycerides and total cholesterol of both sex groups of Type 2 DM with HTN compared to control were found to be highly significance. ($p<0.05$)(31) .

A cross sectional study done in Xiangya Hospital, china, also provide prospective evidence that individuals with higher SUA, including younger adults, are at an increased future risk of T2DM independent of other known risk factors. Hypertensive subjects with CKD had a higher prevalence of hyperuricemia and metabolic syndrome, as well as higher levels of SUA, BMI, waist circumference (WC), SBP, DBP, TG, fasting blood glucose and lower levels of HDL-C. (36).This study also depicted that subjects with metabolic syndrome had 2.16-fold higher ORs of having CKD than those without. Another study conducted in Iran demonstrated that serum uric acid concentration was significantly higher in patients with metabolic syndrome and in T2DM patients. Higher serum uric acid concentrations were associated with a greater probability of albuminuria(32).This study reported a negative relationship between the fasting plasma glucose and the serum uric acid levels, which were in agreement with the findings of other studies.

A retrospective study conducted in Verona, Italy, showed that Subjects with both FPG and triglyceride values exceeding the ATP III criteria thresholds were more likely to be male and had a marked increase in serum uric acid levels (355 μmol/L, 95% CI = 208–555 μmol/L versus 304 μmol/L, 95% CI = 172–494 μmol/L; $P < 0.001$). After stratifying the study population between males and females and after adjustment for age, the results were nearly identical. The study subjects with hyperuricemia (serum uric acid $\geq$ 506 μmol/L for males and $\geq$ 416 μmol/L for females) also had a significantly higher prevalence of abnormal values of both FPG and triglycerides (32% versus 11%; $P < 0.001$) as compared to subjects with normal serum uric acid values. FPG and triglycerides were independently associated with serum uric acid levels after adjustment for age and gender, concluding the mutual biological interrelationship observed between serum uric acid, hypertriglyceridemia and hyperglycemia raises the possibility of a potential pathogenetic overlap between these conditions(33).

In another cross sectional study done in a rural community from Iasi County, Romania, serum uric acid levels are significantly associated with the parameters of metabolic syndrome. There is significant correlations between the serum levels of uric acid and BMI (n=254, r=0.280, p<0.0001), triglycerides (n=254, r= 0.305, p<0.0001), waist circumference (n=254, r= 0.335, p<0.0001) and hip circumference (n=254, r= 0.212, p<0.001). This study also found moderate correlations between the levels of uric acid and total cholesterol (n=254, r= 0.13, p= 0.039), fasting glycemia (n=254, r= 0.11, p= 0.042), systolic blood pressure (n=254, r= 0.122, p= 0.04) and diastolic blood pressure (n=254, r= 0.118, p= 0.041). No significant correlations were found between uric acid and HDL (n=254, r= -0.106, p= 0.093) or uric acid and LDL (n=254, r= 0.039, p= 0.54), which is similar finding with the previous cohort study (34).

According to a community-based prospective cohort study conducted in the Chin-Shan Community done on 2690 non diabetic participants(age range, 35–97 years) and who had no cardiac problem during baseline assessment at study entry, found that High SUA concentrations was associated with a higher prevalence of metabolic syndrome. This study also showed that Uric acid concentration was shown to be inversely correlated with HDL and positively correlated with BMI, waist circumference, triglycerides, and insulin resistance(35).

Case-cohort nested in the European Prospective Investigation into Cancer and Nutrition-Netherlands study confirms that uric acid may be an independent risk factor for diabetes. Although a large part of the association can be explained by the degree of adiposity. This study suggests diet has a minor role as confounder in the association of uric acid with diabetes(36).

According to a cross sectional study conducted on T2DM patients in Lagos, Nigeria, the prevalence rates of hyperuricemia and the MetS were 25% and 60% respectively. The frequency of occurrence of hyperuricemia was comparable in both genders (59% for male vs 41% female, p = 0.3). Although, the prevalence of the MetS in subjects with hyperuricemia and normouricaemia was comparable (61 vs 56% respectively, p = 0.1), a higher proportion of hyperuricemia subjects had three or more components of the Mets compared with normouricemic subjects(26).

A study done in sub Saharan Africa showed that Hyperuricaemia–hypertriglyceridaemia was identified as distinct component in the rural and semiurban group whereas hyperinsulinemia was loaded together with other risk factors. In the entire study population, five factors could be

identified in the following sequence: obesity, hypertension, hyperuricaemia–hypertriglyceridaemia, hyperglycaemia and hyperinsulinaemia. Subjects with hyperuricaemia but not with insulin resistance exhibited an increased risk to develop the metabolic syndrome. this study concluded that Hyperuricaemia was revealed as additional component of the metabolic syndrome in sub-Saharan Africans and should be given more attention in prevention settings(37). A Meta analysis of 11 studies has revealed that every mg/dl increase in uric acid level is associated with 17 % increased risk of diabetes(21).

CHAPTER THREE: OBJECTIVES

3.1. General objective

- ✓ To determine the magnitude of hyperuricemia and its association with Metabolic syndrome(MetS) among Type two diabetes mellitus(T2DM) patients attending hawassa comprehensive specialized hospital (HCSH) from February 28 to May 30 /2017

3.2. Specific objectives

- ✓ To determine the prevalence of hyperuricemia in T2DM patients attending HCSH
- ✓ To determine magnitude of MetS in T2DM patients attending HCSH
- ✓ To assess the association of hyperuricemia with MetS among T2DM patients attending HCSH
- ✓ To assess association of uric acid level with components of metabolic syndrome among T2DM patients attending HCSH

CHAPTER FOUR: MATERIALS AND METHODS

4.1 Study area and period:

The Study was conducted at HUCSH from February to March 2017. This was a cross sectional study carried over a period of 3 months from March 2017 to may 217. The study population consisted of subjects with T2DM who were receiving care at the HUCSH, Southern Nations Nationalities and Peoples Region (SNNPR) from January to June 2017. Hawassa is the capital city of the region and located 275 Km from Addis Ababa, which is the capital city of Ethiopia. The altitude of the town is 1697meters above sea level with the mean annual temperature and rainfall of 20.9^{O}C and 997.6 mm respectively. In addition, the hospital was established in November, 2005 and it serves for more than 10 million people and provides health care services for populations of SNNPR and neighboring regions. There are 2271 registered DM patients. out of which 2050 are type 2 DM and the rest are type 1 DM. This study was conducted in T2DM patients who have regular follow-up at outpatient chronic diseases clinic of the hospital.

4.2. Study design

Institution based cross -sectional study design was implemented.

4.3. Population

4.3. 1.Source population

All T2DM patients attending HCSH diabetic clinic was the source population.

4.3.2 Study population

T2DM patients who visited HCSH Diabetic clinic during the study period and selected for the study after fulfilling the inclusion criteria

4.4. Eligibility criteria

4.4.1. Inclusion criteria

Patients with T2DM who visited HCSH Diabetic clinic during the data collection period and who are voluntary to participate and who gave informed consent was included in the study

4.4.2. Exclusion criteria

- Patients having known history of Acute myocardial infarction, leukemia, gout, alcohol consumption within the past 24 hours
- Patients with known thyroid disorder, renal failure, and hepatic disorder was excluded.
- Pregnant women and those patients receiving blood lipid altering therapy like statins, those patients taking drag for hyperuricemia and contraceptive drugs was excluded.

4.5. Sample size determination and sampling techniques

Sample size was determined using the formula for single population proportion based on the following assumptions,

Estimated proportion (P) taken from a literature review=25.3% (1).
Margin of error d=5%
Confidence interval of 95% is assumed (zα/2=1.96)

n = $(z\alpha/2)2\, p(1-p)/d2$

n= is the size of the sample

Z= is the standard normal value corresponding to the desired level of Confidence

d =Margin of error

P=is the estimated proportion of hyperuricemia in DM patients who have also MetS

n = $(1.96)^2 0.253(1-0.253)/(0.05)^2$ =290

Considering 10% non-respondent rate, the final sample size will be 319.

A simple random sampling technique was implemented.

4.6. Variables

4.6.1. Dependent variable: Uricaemia

4.6.2. Independent variables

Socio-demographic characterstics including age, sex ; clinical characterstics such as cigarette smoking, alcohol consumption , blood pressure and obesity

4.7. Data collection technique and instruments

4.7.1. Socio-demographic, clinical and related data collection

Pre-informed written consent was obtained before running any data collection. Socio-demographic, anthropometrics and other relevant clinical data of the study participants were collected by using structured questionnaire including patients medical records review.

Systolic and diastolic blood pressure (SBP and DBP) was measured from left arm of each subject with a standard adult arm cuff of mercury based sphygmomanometer. The measurement was made by nurses who were working at chronic illness follow-up clinic after patients rested for at least 10 minutes. The precision of the measurment was maintained by using two readings within one minute difference and finally the average blood Pressure (BP) was taken and recorded to assess BP status. If two readings differed by 10 mmHg, the third measurment was taken and then the average of three readings was used. For those with a systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg, blood pressure was measured on a further 2 occasions after resting, and average values was then taken. Anthropometric data (weight and height) was collected according to WHO STEPS manual (38). Height (without wearing shoes) and weight (with wearing light cloths) was measured from the study subjects. In addition body mass index (BMI: Kg/m^2) was calculated by dividing individual's weight (Kg) by height squared (m^2).

4.7.2. Data collection instrument for Anthropometric measurements

Height scale and digital weighing machine was used to measure height and weight respectively, and Body mass index (BMI) was calculated as weight divided by the square of height in meters. Blood pressure was measured using mercury based sphygmomanometer after the subjects had rested for more than 10 min.

4.8. Blood specimen collection and sample analysis

5 milliliters (ml) of venous blood sample was drawn from each study participant after overnight fast and centrifuged at 3000 cycles/min, and then serum was obtained. The serum samples was analyzed for FBS, high density lipoprotein cholesterol (HDL-C), TGs uric acid using A25^{TM} BioSystem Random Access chemistry analyzer.(Linear chemicals, Montgat, Spain). Overnight fasting (8-12 hours) blood serum was directly used to perform the tests or it was transferred in to nunc tubes and then stored at -20^{0}C until the test analysis. Internal quality control for the laboratory determinations was regularly performed.To check calibration, after every 40 samples, 2 control samples were included.

4.9. Data quality management

Before data collection, English version questionnaires were translated to Amharic and then back to English by other person to check for consistency. Finally, Amharic version was used. Training was given for data collectors (three BSc nurses).After collection, all data including laboratory results were checked for completeness and relevance's by principal investigator each day and essential feedback was offered to data collectors.

The proper functioning of instruments, laboratory reagents and technical performance was checked daily by using quality control samples before running patients sample and along with patient samples. If results fall outside established value, the run was repeated. Data was coded, entered and cleaned using epidata version 3.1 data software before exporting to SPSS.

4.10. Data processing and statistical analysis

All data were checked visually, coded and entered into epidata version 3.4 and statistical analysis was performed using SPSS version 20.0 software. Descriptive statistics like frequency and percentage were computed. Categorical variables were expressed as percentages. In addition, evaluation of differences in means of study groups was evaluated using student's t-test and categorical variables was analyzed using chi-square tests and or fisher exact test. In addition, Bivariate logistic regression and multivariate logistic regression was used to determine the association between explanatory variables and the outcome variable. In all cases a value of $p<0.05$ was considered statistically significant and finally the result was presented using text, tables and graphs.

4.11. Ethical consideration

Ethical clearance to conduct the study was obtained from the ethical review committee of College of Health Sciences, Jimma University. This ethical clearance was taken to HCSH clinical director office and a permission letter to conduct the study was given from the clinical director office. Next, the permission letter was given to the HCSH diabetic clinic to conduct the study. Then, the aim, purpose, benefits and method of the study was clearly explained to the participant. The entire study participant was informed that, the data obtained from them was used only for this study purpose, the confidentiality of the data will be maintained and their name will not be recorded. Next, the study participants was informed that they can withdraw from the study at any time and being withdrawn have no any negative impact on their diagnosis and treatment in the hospital. Finally, they are requested to give informed consent to collect data.

4.12. Limitation of the study

The interpretation of the present results is confronted by some limitations. Firstly, the data analysis was restricted to a cross-sectional study. Only a prospective study could confirm the interdependencies of changes in the metabolic syndrome components and serum uric acid levels. Secondly, no serum insulin levels were measured as an index for insulin resistance. As insulin resistance is believed to play a major role in the metabolic syndrome, the inclusion of this variable in our statistical analysis would have been important. On the other hand it is unlikely

that adjustment for insulin resistance could significantly influence our strongest association of serum uric acid and triglyceride

4.13. Plan for dissemination and utilization of results

The findings will be presented to Jimma University and the copy of the result will be submitted to HCSH; it will also be disseminated through publication on reputable journals and presentation on scientific conferences.

4.14. Operational Definitions

Metabolic syndrome (MetS) is defined according to modified United States National Cholesterol Education Program, Adult Treatment Panel (USNCEP-ATP) III guideline. Patients who have at least three of the following risk features to categorize in MetS: abdominal obesity (defined as waist circumference >102 cm in males and >88 cm in females); elevated TGs (≥150 mg/dl); low HDL-c (<40 mg/dl in males and <50 mg/dl in females); elevated blood pressure (SBP ≥130 or DBP ≥85 mmHg) and FBS >110 mg/dl. (39)

Hyperuricemia: Patients having serum uric acid levels more than 7.2 mg/dl in males and more than 6.3 mg/dl in females.(40)

CHAPTER FIVE-RESULT

5.1. Socio demographic and other characteristics of the study participants

A total of 314 T2DM patients were enrolled in the study, of which 211(67.0%)of them were males and the rest were females. The mean age of the participant was 49.8(9.8).Subjects enrolled for the study was in age group of 30 to 80 years. Majority of subjects; 118(37.6%) were in the age group of 41-50 years and 7(2.2%) were age greater than 71 years old (table-1).

From the total 314 study participants, 159(50.6%) of the participant were urban dwellers, 278(88.5%) were married, 63(20.1%) were unable to read and write and 127(40.4%) had secondary or above educational status. majority, 214(68.2%), of them are unemployed. Concerning mode of transportation , majority259(82.5%) were walking on foot or bicycle and only about 55 (17.5%) use vehicle. Concerning physical excercises , 214(68.2) did not perform regular exercise. 33(10.5%) and 32(10.2%) of them were smokers or had smoking history and drinkers or had drinking history respectively. From the total participants, 214(68.2) of them do not perform regular exercise. 33(10.5%) and 32(10.2%) of them were smokers or had smoking history and drinkers or had drinking history respectively (table-1).

Table-1 socio demographic and other characteristics of the study participants

variable	Frequency (%)
sex -male	211(67)
female	103(33)
age mean(SD)	49.8(9.8)
<40	79(25.2)
41-50	118(37.6)
51-60	77(24.5)
61-70	33(10.5)
>70	7(2.2)
Residence- Urban	159(50.6)
rural	155(49.4)
Educ. level -Unable to read write	63(20.1)

	primary	124(39.5)
	secondary and above	127(40.4)
marital status -Unmarried		36(11.5)
	married	278(88.5)
Occupation- Unemployed		214(68.2)
	employed	100(31.8)
Transport mode-Walk/bic		259(82.5)
	- vehicle	55(17.5)
regular exercise- No		214(68.2)
	Yes	100(31.8)
Ever smoking -No		281(89.5)
	-Yes	33(10.5)
Ever drink alcohol- No		282(89.8)
	-Yes	32(10.2)

Clinical, biochemical and other features of the study participants

The prevalence of hyperuricemia was 33.8%. Concerning the prevalence of hyperuricemia among age distribution, its prevalence was highest among age group ≥45 years(61. 8%).the distribution of uric acid level among the age group was statistically significant (p=0.01). A total of study participants which had a family history of Diabetes mellitus accounts 55(17.5%), out of which 25.5% of them are hyperuricemic, while the rest, 259(82.5%) of them, which account 74.5% of hyperuricemic participant, had no family history of DM. the distribution of uric acid level between those who had and hadn't family history of DM was significant(p=0.008). out of the total 314 participants, 66(21.0%) of them had greater than 10 years of duration since first diagnosed of DM, the rest 248(79.0%) being less than 10 years duration and the distribution of uric acid level was not statistically significant(p=0.83). concerning regular exercise, 100(31.8%) of them exercises regular exercise(table-2).

Regarding their body mass index, 11(3.5%) of them had a BMI of less than 18.4, 130(41.4%) of them having a BMI of between 18.5-24.9. majority of the study participants, 114(36.3%), fall under the category of overweight having BMI of between 25-29.9 and 59(18.8%) of them were

having BMI of ≥30 Kg/m2, which make them fall under the category of obese. The study participants had a mean (SD) body mass index of 25.6(4.3) .the study participants who had hyperuricemia had higher mean of BMI (27.8) than those without the syndrome (24.5) in which the difference is significant (p<0.001)(table-2).

Table-2: distribution of uric acid level among different variables

variables		314(%)	uric acid level		p-value
			hyperuricemia	normouricaemia	
sex	male	211(67.2)	70(66.0)	141(67.8)	
	female	103(32.8)	36(34.0)	67(32.2)	0.76
age (in year)	<45	120(38.2)	30(28.3)	90(43.3)	
	≥45	194(61.8)	76(71.7)	118(56.7)	0.01
FHD	-no	259(82.5)	79(74.5)	180(86.5)	0.008
	-yes	55(17.5)	27(25.5)	28(13.5)	
Duration of DM-<=10		248(79.0)	83(78.3)	165(79.3)	
	->10	66(21.0)	23(21.7)	43(20.7)	0.83
regular exercise	-no	214(68.2)	78(73.6)	72(34.6)	
	-yes	100(31.8)	28(26.4)	136(65.4)	0.14
MetS	- no	94(29.9)	19(20.2)	75(79.8)	
	-yes	220(70.1)	87(39.5)	133(60.5)	0.001
mean BMI, Kg/m2, (SD)		25.6(4.3)	27.8(4.0)	24.5(4.0)	
<18.4		11(3.5)	3(2.8)	8(3.8)	
18.5-24.9 Kg/m^2		130(41.4)	20(18.9)	110(52.9)	
25-29.9		114(36.3)	52(49.1)	62(29.8)	
≥30 Kg/m^2		59(18.8)	31(29.2)	28(13.5)	<0.0001
Median WC, cm(IQR)		93.6(18.1)	105.8(17)	88(79-95)	<0.0001
Mean SBP, mmHg(SD)		123.6(14.3)	129.5(15.9)	120.7(12.7)	<0.0001
Mean DBP, mmHg(SD)		79.1(9.2)	81.7(8.8)	77.9(9.2)	<0.0001
Mean FBS, mmHg(SD)		**200(100.1)**	208.8(95)	195.4(103.2)	0.06
Median HDL,mg/dl(IQR)		48.0(38.0-60.3)	51.0(39.0-62.25)	46.0(38.0-57.0)	0.092
Median TG, mg/dl(IQR)		194.5(139.5(246)	245.5(209.8-286)	162.0(127.5-203)	<0.0001
Mean TC, mmHg(SD)		183.7(44.9)	200.9(42.1)	174.9(43.9)	0<0.0001
Mean(SD) uric acid		5.8(2.5)	8.5(2.0)	4.4(1.3)	<0.0001
BP-normal		234(74.5)	62(58.2)	172(82.7)	
-raised		80(25.5)	44(41.5)	36(17.3)	<0.0001

Note: FHD-family history of DM, BMI, body mass index; DBP, diastolic blood pressure;BP,blood pressure, FBS, fasting blood sugar; IQR, interquartile range; HDL-c, high density lipoprotein cholesterol; SD, standard deviation; WC, waist circumference; SBP, systolic blood pressure; TGs, triglycerides; *, significance by fishers' exact test

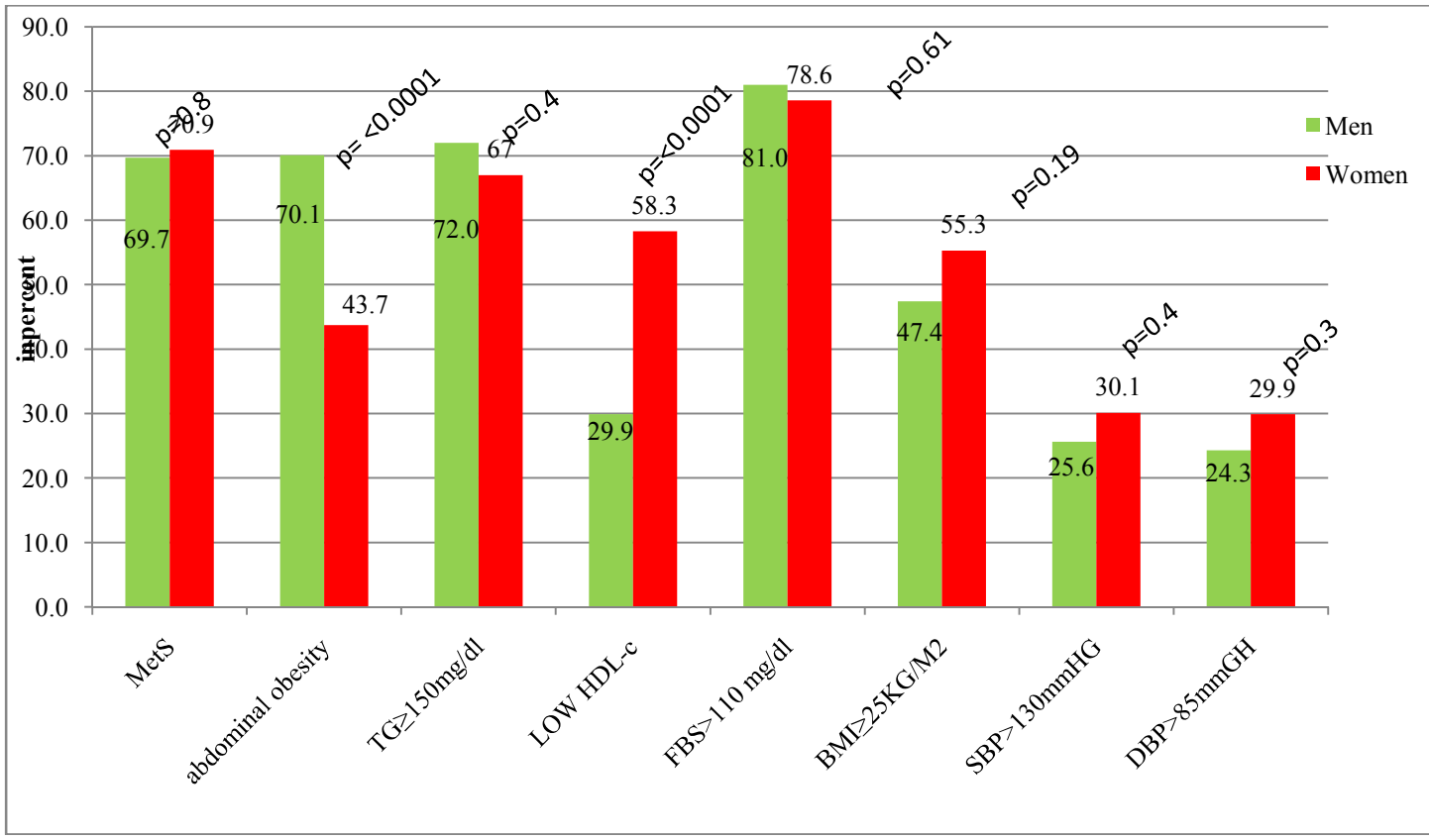
Furthermore, compared with normouricemic group, individuals with hyperuricemia had significantly higher mean (median) values of WC (105 Vs 88, p<0.001), SBP (129.5 Vs 120.7, p<0.001), DBP (81.7 Vs 77.9, p<0.001), FBS (208.8 Vs 195.4, p=0.06), TGs (245.5 Vs 162.0, p<0.001) and median HDL-c (compared to a group with MetS (Table-2)

Out of the total 314 study participants, 220(70.1%) of them had MetS by the criteria of NCEP-panel III. The total prevalence of hyperuricemia among the study participants were 33.8% (106).out of these 106 participants, 87(82.1%) of them had MetS. only 75 participants had no MetS and hyperuricemia and the distribution of MetS among uricaemic participants was statistically significant (p=0.001).

The mean (SD) uric acid level of the study participants were 5.8(2.5).compared to normouricemic group, study participants who had hyperuricemia had significantly higher mean (SD), 8.5(2.0) Vs 4.1(1.3), of uric acid level distribution p<0.001). The prevalence of raised BP was 25.5%and 41.5% of hyperuricemic patients had raised BP (defined as greater than 130/85mmHG or being under hypertensive treatment) and the distribution of BP was statistically significant (p=<0.0001)(table-2).

Pattern of metabolic syndrome and its components in type 2 diabetes mellitus patients' by gender

Metabolic syndrome was diagnosed in 220 patients (70.1%). From the overall prevalence of MetS (70.1%), women had insignificantly higher rate of MetS when compared to men (70.9 % vs. 69.7 %; p=0.8, respectively) based on gender group comparison though the difference of the distribution was not significant (Figure 1).



Note: BMI, body mass index; FBS, fasting blood sugar; HDL-c, high density lipoprotein cholesterol; WC, waist circumference; SBP, systolic blood pressure; TGs, triglycerides;

Figure 1:-distribution of MetS and its components among T2DM in relation of gender

The frequency of MetS components: abdominal obesity, raised triglycerides, raised fasting blood sugar, low HDL-c were 61.3%, 70.4%, 80.0% and 39.2%, respectively. regarding the frequency of SBP and DBP, men had raised SBP(25.6%) than women(30.1%) and women had raised DBP(29.9%) than men(25.6%) though the difference were not significant(p=0.4, and p=0.3).In addition the proportion of abdominal obesity was significantly higher in men when compared to women (p<0.001)(Fig.1).women had higher proportion of reduced HDL-c(58.3%) than men(29.9%) and it is statistically significant(p<0.001) (Figure 1).

Prevalence of metabolic syndrome and its components among diabetic patients in relation to Hyperuricemia

Among the study subjects, out of 106 patients having hyperuricemia; 98(92.5%) patients also had high triglyceride levels leaving only 8 patient with hyperuricemia to have normal level of triglycerides and this difference is statistically significant (p<0.001).compared to normouricemic

patients, patients with hyperuricemia had higher level of FBS (86.8% Vs 76.9%), BMI (76.4% Vs 36.5%), SBP(46.2% Vs 17.3%), DBP(37.7% Vs 23.1%) and the difference is statistically significant($p<0.05$).contrary to these, normouricemic patients had raised level of HDL-c than hyperuricemic patient and the difference is not statistically significant($p=0.4$) (table-3).

Table- 3: Prevalence of metabolic syndrome and its components among diabetic patients in relation to Hyperuricemia

variable	314(%)	Hyperuricemia 106(%)	Normouricaemia, 208(%)	P-value
presence of MetS	220(70.1)	87(82.1)	133(63.9)	0.001
Abdominal obesity(WC≥102 for male, ≥88cm for female	193(61.3)	40(37.7)	153(73.6)	<0.0001
raised TG≥150 mg/dl	221(70.4)	98(92.5)	123(59.1)	<0.0001
reduced HDL-c, (<40mg/dl for males, <50mg/dl for fem)	123(39.2)	38(35.8)	85(40.9)	0.4
raised FBS,(>110 mg/dl)	252(80.0)	92(86.8)	160(76.9)	0.04
raised SBP(> 130 mmHG)	85(27.1)	49(46.2)	36(17.3)	<0.0001
Raised DBP(>85mmHG)	88(28.0)	40(37.7)	48(23.1)	0.006

BMI, body mass index; FBS, fasting blood sugar; HDL-c, high density lipoprotein cholesterol; WC, waist circumference; SBP, systolic blood pressure; TGs, triglycerides;

Factors associated with hyperuricemia

The results of a binary logistic regression model with uricaemia as the dependent variable and MetS components, age, gender, duration of diabetes, family history of diabetes, and others as independent variables are presented in Table-5.

Table-4: Factors associated with hyperuricemia among T2DM patients (logistic regression)

		Uric ACID LEVEL					
variables	**category**	**Hyper uricemia**	**Normou ricaemia**	**COR (95%CI)**	**p-value**	**AOR (95%CI)**	**P-value**
Sex	**female**	36(34.0)	67(32.2)	**1**	0.8		
	male	70(66.0)	141(67.8)	0.9(0.56-1.52)			
Age	**<=45**	30(28.3)	90(43.3)	1		1	0.02
	>45	76(71.7)	118(56.7)	1.9(1.2-3.2)*	0.01	1.9(1.1-3.1)**	
Residence	**urban**	59(55.7)	100(48.1)	1		1	0.1
	rural	47(44.3)	108(51.9)	1.3(0.9-2.2)*	0.20	1.6(0.9-2.9)	
Marit.St.	unmarried	7(6.6)	29(13.9)	1		1	0.14
	married	99(93.4)	179(86.1)	2.29(0.9-5.4)*	0.06	2.0(1.8-4.8)	
Occup.	unemployed	71(67.0)	143(68.8)	1			
	employed	35(33.0)	65(31.2)	1.1(0.7-1.8)	0.8		
Educa. Lev	Unable to re/wri	28(26.4)	35(16.8)	1		1	
	primary	41(38.7)	83(39.9)	0.6(0.3-1.2)*	0.1	0.8(0.4-1.4)	0.4
	secondary and above	37(34.9)	90(43.3)	0.5(0.3-0.9)*	0.04	0.5(0.3-1.0)**	0.04
Smoking	**no**	94(88.7)	187(89.9)	1			
	yes	12(11.3)	21(10.1)	1.1(0.5-2.4)	0.7		
Alcohol	**no**	92(86.8)	190(91.3)	1			
	yes	14(13.2)	18(8.7)	1.60(0.8-3.4)	0.21		
Reg exer	**no**	78(73.6)	136(65.4)	1		1	0.21
	yes	y es	28(26.4)	72(34.6)	0.14		
FHDM	**no**	79(74.5)	180(86.5)	1		1	0.007
	yes	27(25.5)	28(13.5)	2.2(1.2-4.0)*	0.009	2.4(1.3-4.6)**	
DMdur.	**<=10**	83(78.3)	165(79.3)	1	0.8		
	>10	23(21.7)	43(20.7)	1.1(0.6-1.9)			
MetS	Without	19(17.9)	75(36.1)	1		1	0.004
	With	87(82.1)	133(63.9)	2.6(1.5-4.7)*	0.001	2.4(1.3-4.3)**	

Note:*=p<0.2 for COR, **=p<0.05 for AOR, COR-C rude odds ratio,AOR-Adjusted odds ration,FBS-fasting blood sugar; HDL-c-high density lipoprotein cholesterol; WC- waist circumference SBP, systolic blood pressure; TGs,-triglycerides; FHDM-family history of DM, DMdur-duration of DM,Marit.st-marital status, reg ex-regular exercise

From binary logistic regression between uricaemia and some clinical and biochemical parameters such as educational level of being secondary or above, rural dweller, marital status

and educational level had significant association and selected as a candidate for multivariate logistic regression analysis. ($p< 0.2$). From multivariate logistic regression age, educational level of secondary and above, having family history of DM and MetS were found to be possible predictors of the hyperuricemia($p<0.05$) (table-4).

Table 5: Pearson correlation coefficients of parameters of MetS with uric acid level

parameter	Correlation coefficient	P-value
HDL-c	-0.05	0.4
SBP	0.3	0
DBP	0.2	0.006
WC	0.4	0
TG	0.4	0
FBS	0.1	0.5

HDL-C-high density lipoprotein, TG-triglycerides,

From the Pearson correlation coefficient that shows the correlation of hyperuricemia with the components of MetS, except for HDL-C ($p=0.4$) and FBS(0.5), all components are strongly correlated with uric acid level ($p<0.05$) (Table 5).

CHAPTER SIX-DISCUSSION

The main findings of the present study are: first high prevalence of hyperuricemia (33.8%) and MetS (70.1%) among T2DM patients. Secondly, hyperuricemia is strongly associated with Mets (OR=2.4 CI=1.3-4.3 P=0.004) and prevalence of hyperuricemia among study participant who had MetS was higher (82.1% of hyperuricemic patients) than participants who didn't had MetS (17.9%). and lastly hyperuricemia is correlated with only specific components (TG, SBP, DBP FBS and WC) of MetS.

From the present study, the prevalence of hyperuricemia among T2DM was 106(33.8%).this result was comparable with the study from Indore which found the prevalence to be 34.2% and higher than the study done by mundhe et el in India the prevalence being 25.3% (1).The mean (SD) levels of SUA in hyperuricemic and normouricemic subjects was 8.5(2.0) and 4.4(1.3) This finding is comparable with the result done by Antonio ogbera et, el which the mean uric acid level among hyperuricemic and normouricemic to be 8.1 and 4.5 respectively (26).

The prevalence of MetS among T2 DM patients was 70.1%. A study from Cameroon found the prevalence of the MetS defined by IDF to be 71.7% and 60.4% defined by NCEP-ATP III (41) which is relatively comparable to the present study. This result is higher than the study conducted by mundhe et el in which the prevalence was 45.3%(1). The higher rate of prevalence in the present study might be due to the difference in the composition of metabolic syndrome definition or ethnicity variation or because of specific WC cut off value used for indian population(42).another much more lesser prevalence was reported by Victor Mogre and his colleagues, which was 24%(43). The differences could be due to the variable criteria used in defining the MetS as well as ethnic differences. In addition it could be due to the fact that the study did not include HDL and triglycerides as criteria for defining the MetS. The prevalence of MetS done in Thailand, bankok, by Jaipakdee J, et, el showed that it is 18.2% which is another much more less report than the present study. the difference may be explained by because of the study participants were non-diabetic subjects (16).The commonest occurring components of the MetS includes abdominal obesity (61.3%) elevated TG(70.4) and elevated FPG (80.0%) denoting uncontrolled diabetes. this result was closely related with the study done by Mogre et,el other than for TG which found abdominal obesity (77.0%) and elevated FPG (77.0%)(43).

Another important finding of our study was that the prevalence was higher in women (70.9%, n= 73) compared to men (69.7%, n=147) though the difference was not significant. This is in agreement with several studies conducted among T2DM patients in Sub-Saharan Africa(44, 45) and other developing country(46).However, several other studies especially in developed countries have reported contrary findings(47, 48). The high prevalence of the MetS found among women in our study could be due to the fact that a significant proportion of women had reduced HDL-C which is one of the components of the MetS of the NCEP criteria used in this study. Similar reasons have also been given by several studies that have reported higher prevalence of the MetS in women than in men(43, 49).

Hyperuricemia was strongly associated with MetS in T2DM (CI-1.3-4.3, P=0.004).the odds of having hyperuricemia was increased by 2.4 folds for a unit increase in MetS. This result was Consistent with the previous studies (50, 51).A cross-sectional studies done in Egypt, on 200 hospitalized elderly patients found that hyperuricemia was independently associated with MetS (p = 0.023, OR= 3.7) (30).The prevalence of hyperuricemia was higher among diabetic patients with MetS (82.1%) than T2DM patients without MetS(63.9%) and the distribution of hyperuricemia among patients with MetS and without MetS was significant (p=0.01).this result was in line with other studies. Numata et al. reported that uric acid is significantly higher in subjects with the metabolic syndrome when compared to subjects without the syndrome in the Japanese population(52). This was also confirmed by other study (53).

Although the precise mechanisms underlying the association between SUA and MetS remain still largely unknown, hyperuricemia may be partially responsible for inflammatory imbalances in adipose tissues that lead to low-grade inflammation and insulin resistance (54).

A family history of DM, being married, secondary and above educational status, TG, WC, SBP and DBP Were independent predicator variables for prevalence of hyperuricemia in T2DM patients after adjusting for confounding factors.

From the present study, the strong association of Hyperuricemia with MetS hadn't gone the same with all of its components. Hyperuricemia was only associated with WC, SBP, DBP, TG, $p<0.05$.there was no association of hyperuricemia with HDL (P=0.4) and FBS (P=0.5).This result was supported by other studies. Gladys Soans and Roopa Murgod observed a positive correlation between serum uric acid levels with Total Cholesterol and Triglycerides(17). We also

noted that there were more components of the MetS in subjects with hyperuricaemia compared to those with normouricaemia and this result was supported by another study(26).

A significantly higher proportion of subjects had hypertriglycaeridaemia and central obesity ($p<0.001$, $r=0.4$ for both). From our correlation coefficient, TG and WC were found to be positively correlated with SUA. High levels of triglycerides and SUA have each been reported not only to be independently associated with an elevated risk for coronary heart disease but also show strong associations between SUA and triglyceride(55, 56).In our study, the data indicates that serum triglyceride is markedly associated with hyperuricemia ($p<0.001$). Mundhe et,al showed the same results ($p<0.05$)(1).another study by Jamabhorn et, el, also noted that Body mass index, waist circumference, blood pressure, and triglycerides significantly elevated in both men and women with elevated UA levels (all a *p*-value <0.005)(16). There is positive correlation between serum uric acid levels and waist circumference. This was similar to Anthonia Ogbera et al study (26) and sherma et,el study(57).

Hyperuricemia and hypertriglyceridemia are suggested to be associated with insulin resistance syndrome. The association between insulin resistance, hyperuricemia, and hypertriglyceridemia are complicated. This might be expected from the fact that uric acid production is linked to glycolysis and that glycolysis is controlled by insulin.

In our study, it is found that uric acid concentration is positively correlated with elevated SBP and DBP and it is statistically significant ($p<0.05$, $r=0.3$ and 0.2 respectively). Similar correlation was suggested by Mundhe et, el, in which serum uric acid concentration found to be independently correlated with hypertension(1). In our study patients with raised BP, (SBP>130mmHG, DBP>85mmHG) had higher serum uric acid compared with non-hypertensive patients. There was significant correlation between serum uric acid level and raised SBP and DBP which was similar to study by Remedios Shah, although study was done on general population (58). Johnson et al, in their review, have reported a positive association of hyperuricaemia with hypertension in T2DM with complications(2). But a study from Bangladeshi showed an independent association of uric acid level with DBP(59).This different might be due to the small sample size they used.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATION

Conclusion

Our results suggest that hyperuricemia is an associated abnormality that could be considered as a possible marker in those with metabolic syndrome. As hyperuricemia is a common finding in this group of patients, early diagnosis and treatment may be helpful to prevent or decrease the rate of development of overt complications in this population of patients.

Recommendation

From the result of present study, there is high prevalence of hyperuricemia and it is significantly associated with metabolic syndrome in type two diabetes mellitus patients. From this our recommendation will go to:

- ☞ First, for those internist and medical staffs to routinely check for uric acid level of T2DM patients.
- ☞ Second, further study should be conducted with better study design to include uric acid level as one component of MetS.

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ANNEXES

ANNEX-I: QUESTIONNAIRES IN ENGLISH VERSION

A questionnaire prepared to assess the association between hyperuricemia and metabolic syndrome in DM patients at HCSH, 2017.

PART I: questionnaire for Socio-demographic characteristics

Patient code_____

Instruction: for the following question please circle one from the given chooses/write in words.

1. sex 1.men 2.women
2. What is your age? _____year
3. Where do you live? 1. Urban 2. Rural
4. What is your educational status? 1. Illiterate 2. Primary 3. Secondary 4. Tertiary
5. Marital status 1. Single 2. Married 3. Divorced 4. Widowed
6. Occupation 1.Farmer 2.employed 3. Daily labourer 4. House wife 5. Merchant 6.Others specify_____

Part II: questionnaire for associated risk factors and behavioral activities

7. Do you have family history of DM? _____ 1. Yes 2. No
8. Smoking status 1. Never smoking 2. Current smoker 3. Former smoker
9. How often do you drink? 1. Never 2. Once per week 3. ≥ once per week 4. Daily 5.former drinker
10. Duration of DM_____
11. Are u pregnant? (for female participant only) 1. Yes 2. No
12. Mode of transportation 1. Walking or bicycle 2. Motorized vehicle
13. Are you doing regular physical exercise? 1. Yes 2. No
14. Are you on Anti-hypertensive treatment 1.Yes 2.No

PART III: Anthropometric measurnment

15. Height _____(in meter)

16. Weight _____ (in Kg)

17. BMI _____ (in Kg/m^2)

18. Blood pressure_____(SBP/DBP in mmHg)

19. Waist circumference_____

PART IV: Laboratory measurements

20. TG _____

21. CHOL_____

22. HDL _____

23. URIC ACID_____

24. FSG(mg/dl) _____

This is the end of the questionnaire. Thank you very much for taking time to answer these questions. We appreciate your help.

ANNEX II : QUESTIONNAIRE IN AMHARIC VERSION

መጠይቅ ክፍል 1 ፡- የቤተሰብና ማህበራዊ ገጽታ

<u>መመሪያ ፡ የሚሰጠው ምላሽ ከአማራጮቹ አንዱን በመክበብ / በጽሁፍ መሙላት ይሆናል፡፡</u>

1. ጾታ 1.ወንድ 2.ሴት
2. እድሜዎት ስንት ነው? _____ዓመት
3. የሚኖሩት የት ነው? 1. ከተማ 2. ገጠር
4. የት/ት ሁኔታ? 1. ያልተማረ 2. አንደኛ ደርጃ 3. ሁለተኛ ደርጃ 4. ሶስተኛ ደርጃ
5. የትዳር ሁኔታ 1.ያላገባ 2.ያገባ 3.የፈታ 4.የሞተበት
6. የስራ ሁኔታ 1.ግብርና 2.የመንግስት ሰራተኛ 3.የቀን ሰራተኛ 4.የቤት እመቤት 5.ሌላ _____
7. የስራዉ አይነት 1. የእጅ ስራ 2.የቢሮ ስራ 3.የጉልበት ስራ

መጠይቅ ክፍል 2: ኢጋላጪ መንስኤዎች

8. በቤተሰቦ ዉስጥ የስከር ታማሚ አለ? 1.አዎ 2.አይ
9. ያጨሳሉ? 1.አዎ 2.አይ
10. ለ ተራ ቁጥር 6. መልሶ አዎ ከሆነ ምን ያህል ያጨሳሉ1.አሁን አቁሚያለዉ 2.አልፎ አልፎ 3.በተደጋጋሚ
11. መጠጥ ይጠጣሉ? 1.አዎ 2.አይ
12. ለ ተራ ቁጥር 8. መልሶ አዎ ከሆነ ምን ያህል ይጠጣሉ?
13. የስከር ታማሚ መሆንዎን ካወቁ ምን ያህል ግዜ ሆንዎት?
14. እርጉዝ ኖት? 1.አዎ 2.አይ
15. የሰዉነት እንቅስቃሴ በመደበኛነት ይሰራሉ? 1.አዎ 2.አይ
16. የግፊት መዳኒት እየወሰዱነዉ? 1.አዎ 2.አይ

መጠይቅ ክፍል 3: አንትሮፖሜትሪክ ልኬቶች

17. ቁመት
18. ክብደት
19. BMI
20. የደም ግፊት

<u>መጠይቅ ክፍል 4:</u>የደም ምርመራ ዉጠየቶች

21. TG
22. TC
23. HDL-c
24. LDL-c
25. URIC ACID
26. FPG

አመሰግናለሁ!!! <u>ጥያቄየን ጨርሻለሁ!!</u>

ANNEX-III PROCEDURE FOR ANTHROPOMETRIC MEASUREMENT

Weight, Height and Body Mass Index

Height: Height was measured by fixing a tape measure to a wall and measuring the height with a movable headboard, with measures to the nearest centimeter. Patients were asked to stand upright without shoes, with their back against the wall, heels together and eyes directed forward.

Weight: Weight was measured with a weighing machine after asking patients to wear light clothing and weight will be recorded to the nearest 0.5 kg.

Body mass index (BMI) was calculated as weight divided by height square (Kg/m2).

Blood Pressure was measured using a mercury sphygmomanometer after the subjects had rested for more than 10 min. Hypertension was defined according to USNCEP-ATP) III guideline classification.

ANNEX-IV: PROCEDURE FOR VENOUS BLOOD COLLECTION

The blood sample, which was taken for analysis, was obtained from the antecubital vein.

1. First, the subject was told that he is going to give the blood sample and was asked for his permission.
2. Then a sterile, dry, preferably plastic syringe of the capacity required Selected
3. A soft tubing tourniquet or fastening arm band to the upper arm of the subject Applyed.
4. The puncture site was Cleanse with 70% ethanol and allowed to dry. the cleansed area was not re-touched.
5. When sufficient blood has been collected, the tourniquet was released and instructed to open his or her fist. The needle Removed and immediately pressed on the puncture site with a piece of dry cotton wool. The tourniquet Removed completely. The subject Instructed to continue pressing on the puncture site until the bleeding has stopped.
6. The collected blood will be filled in to plane tube and used for the required analysis.
7. Centrifugated, Separated and storage

ANNEX-V: TEST METHODOLOGY AND PRINCIPLES FOR EACH TEST TO BE PERFORMED

The lipid profile of all the patients was tested after an overnight fast that includes testing of total cholesterol, triglyceride, HDL, LDL, levels.

Biochemical analysis

The samples were collected by standard procedures under aseptic conditions. Standard procedures were followed for the preservation and storage of samples before analysis.

Enzymatic colorimetric quantitative Method of total CHOL in serum or plasma

It is measured by CHOD-PAP method**; (**HUMAN Gesellschaft für Biochemica und Diagnostica mbH, Germany: TC intra-assay CV = 1.19%, TG inter-assay CV = 2.53%), enzymatic colorimetric method for Cholesterol with lipid clearing factor (LCF). The Cholesterol is determined after enzymatic hydrolysis and oxidation. Indicator is quinoneimine formed from H_2O_2, 4-aminophenazone in the presence of and phenol and peroxidase.

Cholesterol esterase

Cholesterol esters+H_2O → Cholesterol +fatty acids

Cholesterol oxidase

D CHOL+O_2 →cholest-4en-3-one+H_2O_2

POD

$2H_2O_2$+hydroxybenzoate+4-Amminoantipyrine →red complex +$4H_2O$

The intensity of the red complex is proportional to the total cholesterol present in the sample.

Similarly, HDL-cholesterol (Direct enzymatic method), Triglyceride (GPO/PAP method) and uric acid (Uricase/POD method) levels were measured using standard autoanalyser.

Below are the general test principle of TG, HDL, LDL AND uric acid respectively.

Test Principle of TG

Triglycerides are composed of three fatty acids and a glycerol moiety. Analyzing a serum or plasma sample for triglycerides typically involves four reactions.

The Reaction

Lipase Triglycerides → 3 fatty acids + glycerol

Glycerol Kinase Glycerol + ATP → glycerol-3-phosphate + ADP

Principle of the method for direct determination of HDL

The cholesterol from_LDL VLDL and chilomicrones is broken down by the cholesterol oxidase in an enzymatic accelerated non-color forming reaction. The detergent present in the reagent B, solubilized cholesterol from HDL in the sample. The HDL cholesterol is then photometrically measured by means of coupled reactions described below.

CHOL esterase Cholesterol esters $+H_2O$ →cholesterol +fatty acid

CHOL oxidase Cholesterol$+1/2O_2+H_2O$ →cholestenone$+H_2O_2$

Peroxidase $2H_2O_2$+4-Aminoantipyrine+DSBmT →Quinoneimine $+4H_2O$

Uric acid

Uricase Method

Uric acid + H2O + O2 →allantoin + CO2 + H2O2

Plasma glucose level

Glucose oxidase method will be used.

ANNEX-VI: INFORMATION SHEET IN ENGLISH VERSION

Information sheet

Purpose

The aim of this study is to assess the association of hyperuricemia with metabolic syndrome in DM patients. Your feedback on this research is important, and help prevents further complication due to hyperuricemia on DM patients.

Participation

We are asking you and others to participate voluntarily in this study. We expect from everyone to respond some question, which take about five minutes. Moreover, we will request you to give blood sample for analyzing of TG, HDL, LDL, CHOL and uric acid.

Benefits

If there is important finding during investigation, the result will be attached to your history, opportunities for management will be arranged and you will be followed. you do not pay for any testes and not get paid.

Confidentiality

All the data obtained will be kept strictly confidential by using only code numbers, which is filled by the investigators, and locking the data.

Right to refuse

Since participation in this study is entirely voluntarily, you can withdraw to participate in this study at any time. Your refusal does not affect your medical services.

If you have any question concerning the study, you can communicate with the following address

Principal investigator: Temesgen Bizuayehu

Address: Hawassa University College of medicine and health science Department of Medical Laboratory Sciences.

Tel: 0916604551, E- mail: temesgenbizuayehu2@gmail.com Hawassa, Ethiopia

ANNEX-VII: INFORMATION SHEET IN AMHARIC VERSION

<u>ለጥናቱ መረጀና መግለጫ ቅጽ</u>

የጥናቱ አላማ

የዚህ ጥናት አላማ መሰረት ያደረገው ዩሪክ አሲድ ከሜታቦሊክ ስይንድረም ጋር ያለውን ቁርኝት በስኩር ታማሚዎች ላይ ለማጥናት ነው፡፡ እርሶ በዚህ ጥናት መሳተፎ የስኩር ታማማሚዎች ዩሪክ አሲድ በደም ዉሰጥ መብዛት የሚያስከትለዉን ተጨማሪ ህመም ለመቆጣጠር ይረዳል ::

በጥናቱ ስለመሳተፍ

በዚህ ጥናት መሳተፍ በሙሉ ፈቃደኝነት ላይ የተመሠረተ ነው፡፡ ስለሆነም በመጀመሪያ በጥናቱ እንዲሣተፉ ፈቃደኝነተዎን በትህትና እንጠይቃለን፡፡በዚህ ጥናት ለመሳተፍ ከፈቀዱ ለአመስት ደቂቃ ያህል ለጥያቄዎች ምላሽ ይሰጡናል፡፡ በተጨማሪም ለተለያዩ ምርመራዎች የደም ናሙና ለመስጠት ፈቃደኛ እንዲሆኑ እንጠይቆታለን፡፡

በጥናቱ በመሳተፍ የሚገኝ ጥቅም

የደመዎ ናሙና በላብራቶሪ ሲመረመር ጠቃሚ ዉጠየት ካለ ከ ዶክመንቶ ጋር ዕንዲያያዝ እና የህኪም ክትትልና አስፈላጊውን ምክር እንዲሰጦ ይደረጋል፡ ፡ በዚህ ጥናት ላይ በመሳተፎ የሚከፍሉትም ሆነ የሚከፈሎት ክፍያ አይኖርም ፡ ፡

ምስጢርን ስለመጠበቅ

በጥናቱ ውሰጥ የተሰበሰቡ ማናቸውም ግላዊ መረጃዎች ሚስጥራዊነታቸው የተጠበቀ ይሆናል፡ ፡ ከማንነትዎ ጋር በቀጥታ ተያያዥነት ያላቸው መረጃዎች በሙሉ በዋና ተመራማሪው ሚስጥራዊ በሆነ የመረጃ ጥንቅር ዘዴ ከተቀየሩ በኋላ ብቻ ለምርምር ሂደቱ የሚውሉ ይሆናሉ፡ ፡

ከጥናቱ ስለመውጣትና ስለማቋረጥ

ይህ ጥናት በፈቃደኝነት ላይ የተመሰረተ እንደመሆኑ መጠን ጥናቱ ዉስጥ አለመሳተፍና በማናቸውም ወቅት በፈቃደዎ ከጥናቱ መወጣት ይችላሉ፡ ፡ ከጥናቱ በመዉጣቶ በህክምናዎ ላይ ምንም አይነት ችግር አያመጣም ፡ ፡

ከጥናቱ ጋር በተያያዘ ማናቸውም ጥያቄ ቢኖርዎ በሚከተለው አድራሻ ጥያቄዎን ማቅረብ ይችላሉ፡ ፡

ዋና ተመራማሪ፡- ተመስገን ብዙአየሁ **አድራሻ፡** ሀዋሳ ዩኒቨርስቲ ሜዲካል ላቦራቶሪ ሳይንስ ትምህርት ክፍል

ሀዋሳ፣ ኢትዮጵያ ስልክ : 09-16-60-45-51፤ ኢ-ሜል : temesgenbizuayehu2@gmail.com

ANNEX VIII: CONSENT FORM ENGLISH VERSION

(*To be translated to Amharic*)

Code No_____

I consent acceptance, has been explained to me in a language I understand on hyperuricemia and its association with MetS among DM in our country. I understand that hyperuricemia and its association with metabolic syndrome in DM patients is not well known. For this reason, doing research on this title will be paramount important to decrease the complication.

Therefore, I am informed about giving blood sample in no harm method and I will be interviewed for five minutes. More over all the data obtained will be kept strictly confidential. Anonymous testing will be undertaken, that is sample will be coded and result will not be identified by names in this paper and in the other reports; decline to answer the questions; the right not to participate or withdraw and decide not to participate has no influence on any services that I seek to get. Even I have been assured that I am benefited from cost free laboratory examination and based on the test result I will get the usual professional support from the assigned physician.

Therefore, by understanding the objective of the consent, I agreed to give blood sample for the stated purpose and I have no any objection if this sample also used for similar research in the future. Participating in this study is purely voluntarily; I am very happy and I have informed this to the consent offering personnel.

For this, I declared with my signature.

Consent acceptor signature (no name) _____witness signature ____Person Obtaining Consent__

Date _____ Date_____ Date_____

Researchers address

Temesgen Bizuayehu; Hawassa University Tel. 09-16-60-45-50

ANNEX IX: CONSENT FORM AMHARIC VERSION

ስለስምምነቱማረጋገጫ

የሚስጥርቁጥር _____

እኔ ውልተቀባይየዩሪክአሲድበደምዉስጥመብዛትጉዳትየሚያስከትልመሆኑንእኔበሚገባኝ ቋንቋተነግሮኝተረድቻለሁ:: የዚህጎመምስርጭት በበቂመጠን እንደማይታወቅና በዚህም ምክኒያት በሽታውን በተመለከተ ይህንን ጥናት በማካሄድ የበሽታውን ስርጭት መጠን ለመቀነስ የሚደረግ ጥረት አጋዥእንደሆነ በሚገባ ተረድቻለሁ ::

ስለዚህም ለተለያዩ ምርመራዎች የደም ናሙና መስጠት እንዳለብኝ ና ለአምስት ደቂቃ ኢንተርቪው መደረግ እንዳለብኝ ተነግሮኛል:: በተጨማሪም የኔ ስምና አድራሻ በዚህ ጹሁፍም ይሁን በሌላ በሚደረግ ሪፖርት እንደማይገለጹ ለምጠየቀውም ጥያቄ ያለመመለስ ብፈልግም በምርምሩ መሳተፍ ወይም አለመሳተፍ መብቴ የተጠበቀ መሆኑንና ላለመሳተፍ ብወስን ምንም አይነት ተፅዕኖ እንደማይኖረው ተረድቻለሁ:: እንዲሁም ናሙናውለተባለው አላማ እንደሚውል በሚደረገውነፃ ምርምራአገልግሎት ተጠቃሚልሆን እንደምችልና በውጤቱም መሰረት ከተመደበው ህኪም የተለመደውን መያዊ እርዳታእንደማገኝ ተረድቻለሁ ::

ስለዚህ የዉሉን አላማ በሚገባ በመረዳት የሰጠሁትን የደም ናሙና ለተባለው ምርምር ና በተጨማሪም ለወደፊቱ ናሙናዉለተመሳሳይ ምርምር ቢያውሉት ተቃውሞ እንደሌለኝ ፣ በጥናቱ መሳተፌ በሙሉ ፍቃደኝነት እንደሆነ ፣ በፍቃደኝነት በመተባበሬ ዐኔ ና ወገኖቼን ልረዳ በመቻሌ ደስተኛ መሆኔን ለውል ሰጪውገልጫለሁ ::

ስለዚህምበፊርማዬ አረጋግጣለሁ ::

የውልተቀባይፊርማ (ስምአይፃፍም)_____የምስክርፊርማ_____የውል ሰጪ ፊርማ_____

ቀን___ ቀን ___ ቀን ___

የተመራማሪውአድራሻ

ተመስገን ብዙአየሁ ፣ ሀዋሳ ዩኒቨርሲቲ ስልክ ቁጥር 09-16-60-45-51

Declaration

I, the undersigned, declare that this thesis is my own work and it has not been presented in other universities, colleges or other institutions for similar degree or other purpose. Where other peoples work has been used, it has been carefully acknowledged and referenced in accordance with the requirements.

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