ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Study On The Association Between TSH Values And Estimated Glomerular Filtration Rate (eGFR) Levels In Euthyroid Patients Of Metabolic Syndrome (MetS).

Vinodha J[1], Chitra Siva Sankari G[2]*, Mukila UD[3], Udaya Kumari G[4], and Preethi A[5].

[1]Assistant Professor, Department of Biochemistry, Govt. Kilpauk Medical College, Chennai, Tamil Nadu, India.
[2]Assistant Professor, Institute of Biochemistry, Madras Medical College, Chennai, Tamil Nadu, India.
[3]Final year M.B.B.S Student, Govt. Kilpauk Medical College, Chennai, Tamil Nadu, India.
[4]Assistant Professor, Department of Biochemistry, Govt. Kilpauk Medical College, Chennai, Tamil Nadu, India.
[5]Assistant Professor, Department of Biochemistry, Govt. Kilpauk Medical College, Chennai, Tamil Nadu, India.

ABSTRACT

This cross-sectional study was performed with the aim of studying the association between TSH values and estimated-GFR (eGFR) levels in euthyroid patients of Metabolic Syndrome. Hence the study was performed in 94 euthyroid individuals with Metabolic Syndrome . The study was conducted in the department of Diabetology, department of General Medicine and department of Biochemistry. It is found that there is a positive correlation observed between TSH values and eGFR levels in euthyroid cases with metabolic syndrome. There is also a statistically significant negative correlation between uric acid values and eGFR levels in euthyroid cases with metabolic syndrome. Further studies to evaluate the relationship of uric acid, TSH with eGFR in metabolic syndrome patients should be undertaken to confirm the results of our study.

Keywords: Metabolic syndrome**,** Thyroid stimulating hormone(TSH), estimated glomerular filtration rate (eGFR), euthyroid patients, uric acid

https://doi.org/10.33887/rjpbcs/2023.14.2.8

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Increased Visceral adiposity was primarily involved in the development of MetS, thus indicating that high calorie intake as a major cause for MetS. The wide distribution and increased incidence of metabolic syndrome in developing countries indicate that the lifestyle About 25% of the adult world population are estimated to have Metabolic Syndrome (MetS) as per the International Diabetes Federation[1]. The components of MetS comprise dyslipidemia (high triglycerides and low HDL cholesterol), central obesity, impaired fasting glucose, and elevated blood pressure[2]. Central obesity, insulin resistance, low-grade chronic inflammation and oxidative stress are implicated in etiology and progression of MetS[3], leading to an increased risk of developing chronic kidney disease(CKD) and other conditions like cardiovascular diseases(CVD), stroke etc.[4] and environmental factors like excess calorie intake and lack of physical activity are the major contributors to developing metabolic syndrome in addition to genetic cause[5]

The risk for CKD is increased progressively with increase in the number of components of the MetS[6]. Each component of MetS is associated with CKD incidence and progression[7]. A decrease in estimated glomerular filtration rate(eGFR), which is a surrogate for the development of CKD, provides strategies for early diagnosis and prevention of CKD[8]. It was also reported by Lee YK et al. that serum TSH concentrations within the normal reference range (euthyroid) were significantly positively correlated with the prevalence of MetS[9]. Other the patients might have thyroid receptor resistance leading to elevated TSH levels. Garduno-Garcia et al., in a study involving 3,148 people , reported that increased TSH within the euthyroid ranges caused a significant increase in the frequency of MetS[11]. . Nathalie E Heima in a cohort study in a representative sample of Dutch older persons involving 1187 subjects found that subjects in the upper quartile with a serum TSH level above 2.28mU/l had a significantly increased prevalence of metabolic syndrome compared with subjects in the lowest quartile with a serum TSH below 1.04mU/l and there was an association between metabolic syndrome and serum TSH in a serum TSH range of 0.3–10mU/l[12].

Zhang et al. in his cohort study demonstrated that TSH within euthyroid range and low-normal levels of FT3 in euthyroid individuals were associated with an increased risk of CKD. studies state that high TSH is associated with increased risk of central obesity, elevated blood pressure, BMI, LDL and uric acid levels[9] as well as triglyceride[10] level. In metabolic syndrome.

Thus these results suggest that these variations in TSH and FT3 levels, even within the normal range, may affect kidney function[13].Ming-Tsung Sun et al. described that TSH can be utilised as an independent factor of the CKD irrespective of body mass index, blood pressure, waist circumference, lipid profile, and fasting blood glucose[14].Studies reported that FT3 levels were positively correlated with eGFR and negatively correlated with serum creatinine levels[15]. FT3 levels are reported to reduce as the severity of renal damage increases . Low-normal levels of FT3 in euthyroid individuals from South Korea were associated with an increased risk of chronic kidney disease in a large cohort study[13].

Uric acid (UA), which is elevated in MetS, also inhibits Nitric oxide production, thus it contributes to endothelial dysfunction[16]. Renal microvascular endothelial dysfunction increases glomerular capillary wall permeability and albuminuria, and it may also promote glomerular capillary loss [17] in prolonged MetS and lead to the progression of renal injury[18]. Jalal D. et al. reported the harmful effect of high serum UA level on new-onset chronic kidney disease in individuals with normal renal function (eGFR >40 and/or >60 ml/min/1.73 m^2) and, this effect of UA has been independent of age, gender, BMI, HT, hypertriglyceridemia, type 2 diabetes, and MetS[19].

Thus, elucidating the association between TSH and eGFR could facilitate an early diagnosis of renal dysfunction, by routine monitoring of renal functions in euthyroid patients of MetS with high TSH. Hence this study is undertaken to evaluate the association between TSH values and estimated-GFR (eGFR) levels in euthyroid patients of MetS so as to evaluate TSH as a biomarker and risk factor for renal dysfunction.

Aim

To study the association between TSH values and estimated-GFR (eGFR) levels in euthyroid patients of Metabolic Syndrome

Objectives

- To estimate the serum TSH and creatinine values in euthyroid patients of metabolic syndrome
- To calculate estimated-GFR (eGFR) from serum creatinine value
- To elucidate the association between TSH values and eGFR levels

MATERIALS AND METHODS

This Cross-sectional study was carried out in the department of General Medicine, Department of Diabetology and Department of Biochemistry in our tertiary care centre after obtaining institutional ethical committee approval and informed consent from the participants.

Study period: Two months

Sample Size Calculation:

Sample size was calculated as follows[for cross-sectional study]

$$n = Z\alpha/2^2 * p *(1-p) / d^2$$

$Z\alpha/2 = 1.96$
p =0.446 [2]
d =0.1115
On substituting the values, n=76(minimum)

Sample size was calculated as follows [for Correlation study]

$$n = [(Z\alpha + Z\beta)/C]^2 + 3$$

$Z\alpha = 1.96$ (α=0.05)

$Z\beta = 0.8416$ (β=0.2)

r =0.29 [1] (r=coefficient of correlation)

c =0.5 x ln [(1+0.29)/(1-0.29)]=0.2986 On substituting the values,n=90(minimum)

Hence minimum sample size(n) is 90

Sample size(n) in our study is 94

Study Population

Inclusion Criteria

Patients of age 18-65years, attending diabetology and Medicine OPD, diagnosed with Metabolic Syndrome.NCEP-ATP III consensus criteria, as mentioned below, were used as diagnostic criteria for metabolic syndrome. Patients with three or more criteria are diagnosed as metabolic syndrome.

a. Central obesity: waist circumference >102cm(male), >88cm(female)
b. Hypertriglyceridemia: triglyceride level ≥150mg/dl or specific medication for this condition
c. Low HDL cholesterol:HDL levels <40mg/dl (male),<50mg/dl (female) or specific medication for this condition

d. Hypertension:blood pressure ≥130mmHg systolic or ≥85mmHg diastolic or specific medication for this condition

e. Fasting plasma glucose level:≥100mg/dl or specific medication or previously diagnosed type 2 diabetes

Exclusion Criteria

a. Patients who did not meet the criteria for MetS
b. Patients with eGFR level <40ml/min/1.73 m^2
c. Patients with TSH level not in the euthyroid range (0.1–5microIU/mL)
d. Patients who have history of thyroid disease, or taking medication for thyroid disease, or antiepileptic drugs
e. Pregnant women

Measurements*

Anthropometric Measurements:

- Weight(kg).
- Height(m).

BMI Measurement:

- BMI= weight in kg/height in m^2

Waist circumference Measurement:

Waist circumference was measured using measuring tape at narrowest point between lower border of lowest ribs, iliac crest at the level of umbilicus, at the end of quiet inspiration with both feet touching and arms hanging freely.

Blood Pressure Measurement:

Systolic and diastolic BP were measured

- Blood pressure was measured after participants had rested at least 5 minutes in sitting posture on the leftarm using sphygmomanometer.
- Blood pressure was measured twice at an interval of 1 minute, mean of two readings considered

Sample Collection

Under aseptic conditions, 5 ml of blood was collected by venepuncture after 10-12 hours of fasting. Blood was immediately centrifuged, plasma, serum was separated. TSH, FT3, FT4 was analysed in fully automated immunoanalyser roche e411. Plasma glucose, serum creatinine and lipid profile were analysed using fully automated clinical chemistry random access analyser roche c311.

Laboratory Investigations:

Thyroid Hormone

Method: Chemiluminescence immunoassay.

Reference Range

TSH:0.1-5microIU/ml
FT3:2.1-4.4pg/ml
FT4:0.8-2.7ng/dl

Creatinine Estimation

METHOD: Modified Jaffe's reaction

eGFR Calculation

Modification of diet in renal disease (MDRD) equation:

eGFR(ml/min per $1.73m^2$) =$186.3 \times (SCr)^{-1.154} \times (Age)^{-0.203}$

multiply by 0.742 for women

Normal value: ≥90ml/min/$1.73m^2$

OTHER BIOCHEMICAL INVESTIGATIONS:

Fasting blood glucose Estimation

METHOD: GOD-POD method (Enzymatic, End point analysis)

Lipid Profile

Serum High-Density Lipoprotein (HDL), Serum triglycerides(TGL), total cholesterol measured.

HDL Estimation

METHOD: Direct, Enzymatic colorimetric method

Triglycerides Estimation

METHOD: oxidase peroxidase method(GPO-PAP Endpoint)

Total cholesterol Estimation

METHOD: cholesterol oxidase-peroxidase method (CHOD-PAP endpoint)

Very low-density lipoprotein

METHOD: calculation by formula

VLDL=TGL/5

Low-density lipoprotein:

METHOD: calculation by formula

LDL=CHOL-HDL-VLDL

Uric acid

METHOD: Uricase method

Normal Value:
male:3.5–7.0mg/dl
Female:2.5-6.5mg/dl

Statistical Analysis

Collected data was entered in MS-Excel and statistical analysis was performed using SPSSv29 package:

ISSN: 0975-8585

a. TSH, the related variables, and eGFR is expressed as mean with standard deviation.
b. Correlation and regression analyses is performed to reveal the association between TSH(with other independent factors) and eGFR.
c. p value <0.05 is considered statistically significant for all statistical analyses.

OBSERVATION AND RESULTS

Table 1. Laboratory variables of all cases with metabolic syndrome (MetS).

PARAMETER	mean ± SD	median	Minimum	Maximum
Triglyceride (mg/dl)	211.287 ± 104.3377	184.000	72	520
HDL (mg/dl)	47.968 ± 10.1308	47.000	27	82
Total cholesterol (mg/dl)	202.894 ± 46.1467	205.500	87	328
Serum Creatinine (mg/dl)	0.849 ± 0.2024	0.800	0.5	1.6
Uric acid (mg/dl)	4.828 ± 1.4841	4.500	2.3	10.2
FT3 (pg/ml)	4.4224 ± 0.76721	4.2850	2.40	7
FT4 (ng/dl)	1.43743 ± 0.280609	1.36000	0.698	2.300
TSH (microIU/ml)	2.36919 ± 1.005487	2.15500	0.550	4.690
eGFR (ml/min/1.73m²)	85.68972 ± 17.745902	89.68752	45.332	140.789

The study population consisted of 30 % (n = 28) males and 70 % (n = 66) females, with mean age of 54.5 ± 9 years. Levels of biochemical parameters; triglyceride, HDL, total cholesterol, serum creatinine, uric acid, free T3, free T4, TSH and eGFR were 211.287±104.3377, 47.968 ± 10.1308, 202.894 ± 46.1467, 0.849 ± 0.2024, 4.828 ± 1.4841, 4.4224 ± 0.76721, 1.43743 ± 0.280609, 2.36919 ± 1.005487 and 85.68972 ± 17.745902 respectively.

ISSN: 0975-8585

Table 2. Correlation between eGFR and other variables in Metabolic syndrome

	Pearson's correlation coefficient	p	Partial Correlation coefficient (r)	p
Triglyceride (mg/dl)	-0.071	0.495	0.033	0.758
HDL (mg/dl)	-0.092	0.376	-0.047	0.663
Total Cholesterol (mg/dl)	-0.181	0.081	-0.064	0.556
Uric acid (mg/dl)	-0.417	<0.001	-0.416	< 0.001
FT3 (pg/ml)	0.206	0.046	0.158	0.142
FT4 (ng/dl)	-0.050	0.630	-0.122	0.259
TSH (microIU/ml)	0.203	0.050	0.156	0.146

r: the partial correlation coefficient, $p < 0.05$ was considered significant. Partial correlation between TSH and eGFR is r=0.156

Partial correlation between FT3 and eGFR is r=0.158 Partial correlation between FT4 and eGFR is r=-0.122 Partial correlation between HDL and eGFR is r=-0.047

Partial correlation between total cholesterol and eGFR is r=-0.064 Partial correlation between triglycerides and eGFR is r=0.033

Table 3: Multiple linear regression model with estimated-GFR:

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	7418.901	7	1059.843	4.168	<.001[b]
	Residual	21868.385	86	254.284		
	Total	29287.286	93			

a. Dependent Variable: eGFR

b. Predictors: (Constant), TSH, FT4, Uricacid, HDL, TAG, FT3, Cholesterol

The multiple regression between eGFR and TSH with other variables is found to be significant (p<0.005)

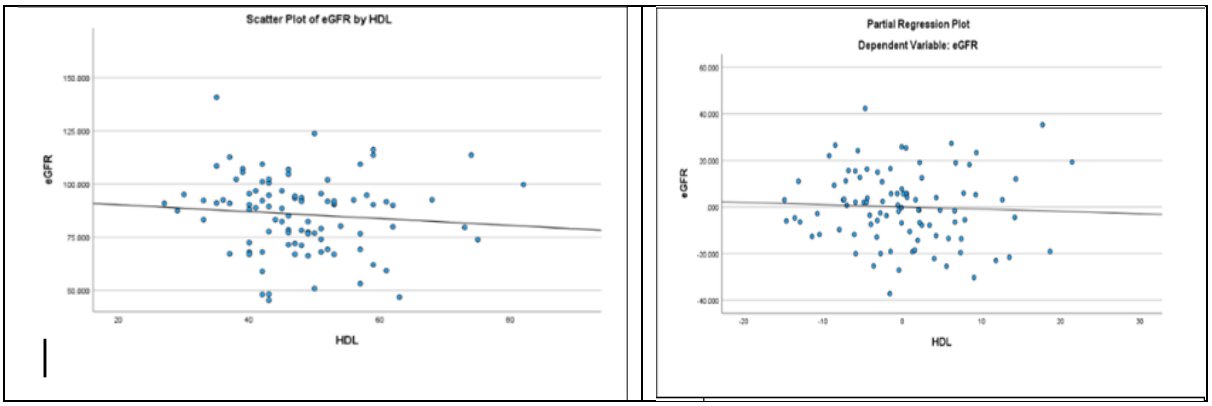
ISSN: 0975-8585

Table 4: Multiple linear regression model with estimated-GFR

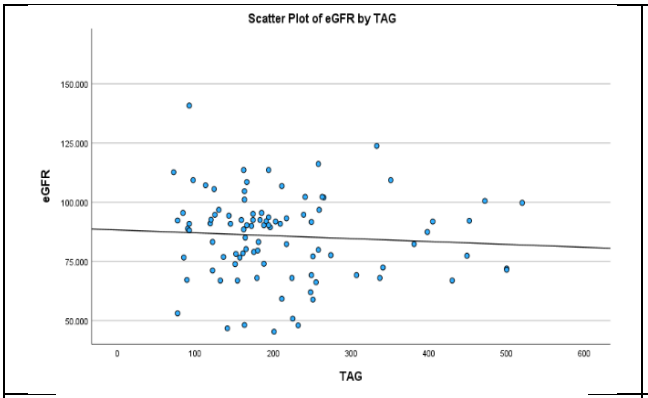
DEPENDENT VARIABLE	INDEPENDENT PREDICTORS	b	t	P
eGFR	Triglyceride (mg/dl)	0.034	0.309	0.758
	HDL (mg/dl)	-0.055	-0.437	0.663
	Total Cholesterol (mg/dl)	-0.083	-0.591	0.556
	Uric acid (mg/dl)	-0.408	-4.248	< 0.001
	FT3 (pg/dl)	0.148	1.483	0.142
	FT4 (ng/dl)	-0.109	-1.137	0.259
	TSH (microIU/ml)	0.145	1.467	0.146

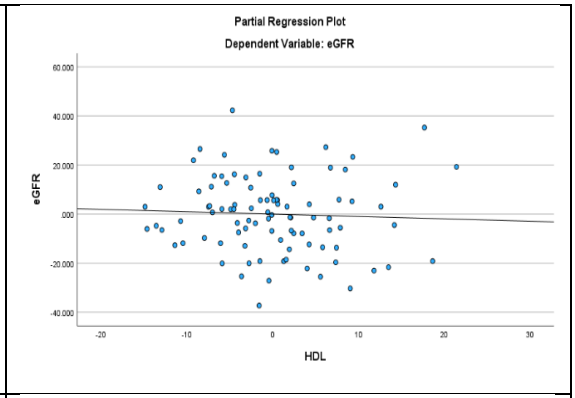
b; standardized coefficients, t: t value, p < 0.05 was considered significant. In multiple linear regression, Regression between FT3 and eGFR is b=0.148 Regression between Triglyceride and eGFR is b=0.034
Regression between HDL and eGFR is b=-0.055
Regression between total cholesterol and eGFR is b=-0.083
Regression between Uric acid and eGFR is b=-0.408
Regression between FT4 and eGFR is b=-0.109
Regression between TSH and eGFR is b=0.145

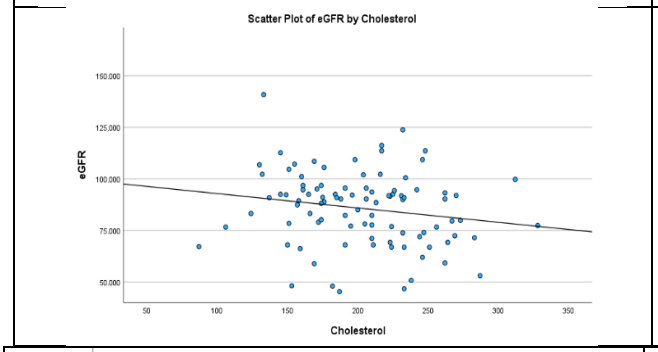
Table 5: Scatter plot and partial regression plot between eGFR and other variables:

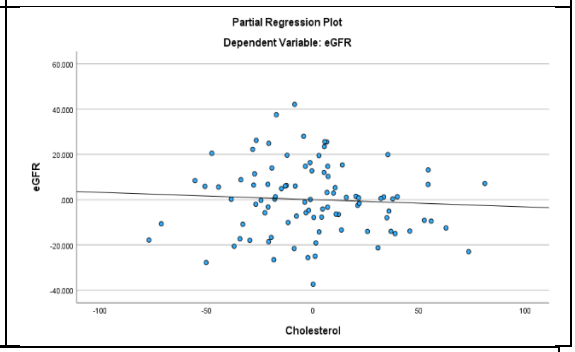


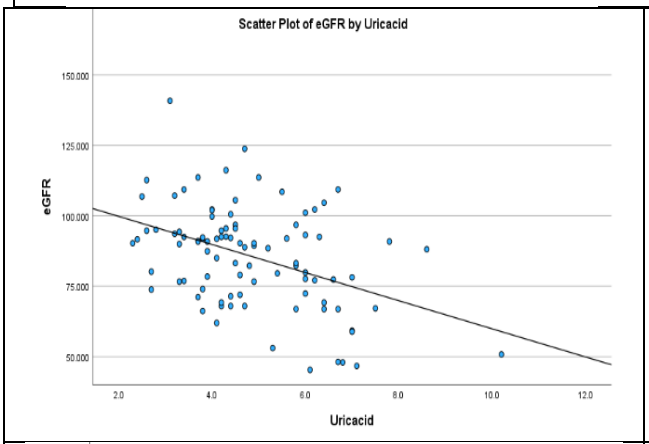
ISSN: 0975-8585

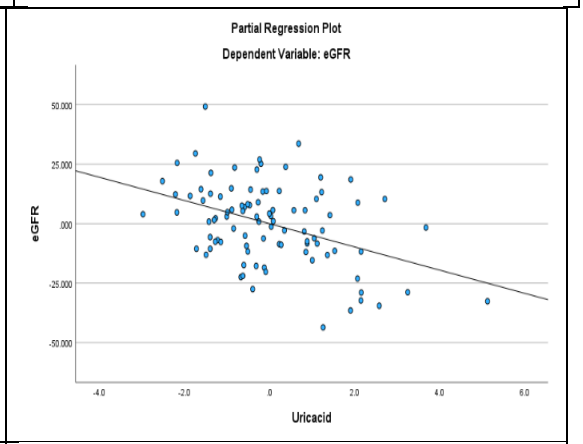


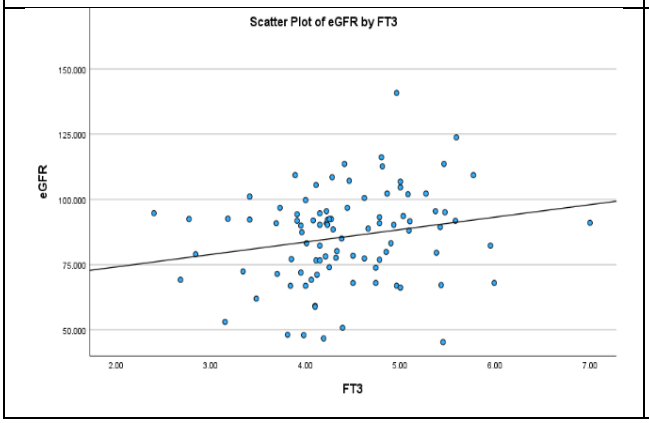


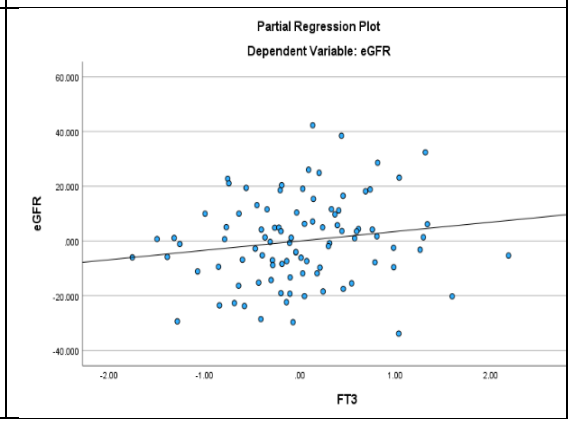




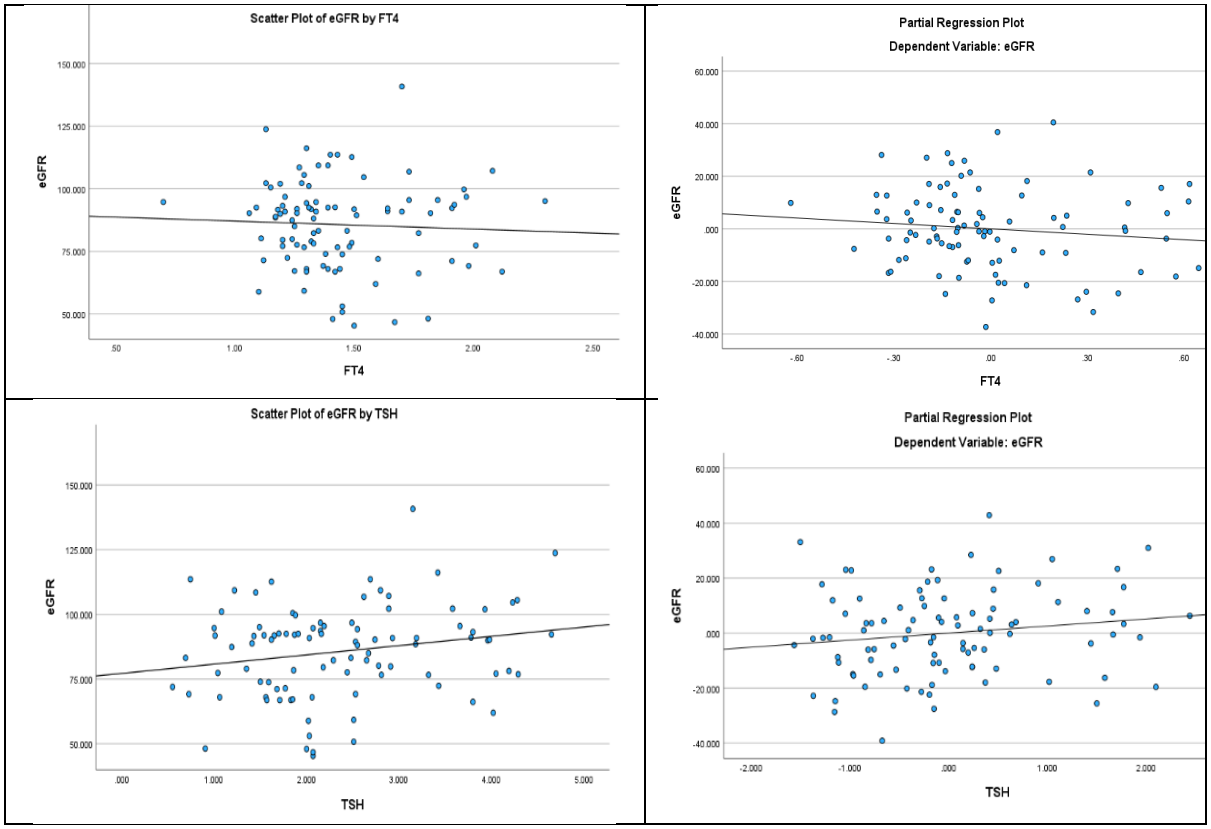








ISSN: 0975-8585



All the patients were known cases of type 2 diabetes mellitus and hypertension and were on medication.

DISCUSSION

The purpose of this study was to find if there is an association between TSH and eGFR in euthyroid cases of metabolic syndrome. Hence this cross-sectional study is performed in 94 euthyroid individuals with metabolic syndrome. This study was conducted in department of Diabetology, department of General Medicine and department of Biochemistry.

Patients who did not meet the criteria for metabolic syndrome, whose eGFR level is <40ml/min/1.73 $m^{2,}$ those with TSH level not in the euthyroid range (0.1–5microIU/mL), those with history of thyroid disease, or taking medication for thyroid disease, or antiepileptic drugs and pregnant women were excluded from this study.

TSH levels observed in this study in euthyroid individuals with metabolic syndrome is 2.36919±1.005487 (median=2.15500) whereas other studies noted a value of 1.58(median) (range 0.50–4.50) in metabolic syndrome patients [1]. The TSH value in this study in euthyroid metabolic syndrome patients is within the reference range (0.1-5microIU/ml).

The estimated-GFR value calculated using serum creatinine in euthyroid patients with metabolic syndrome is 85.68972 ± 17.745902, (median=89.68752), whereas Keskin H et al. in his study observed a value of 94.3 (median) (range 41.3–194) [1] . The mean eGFR value in our study was lower than the normal value of eGFR (>90ml/min/1.73m^2) indicating that most of the euthyroid metabolic syndrome patients are progressing towards kidney dysfunction.

In this study performed in euthyroid patients of metabolic syndrome, the FT3 value is found as 4.4224 ± 0.76721 (median=4.2850) which was higher than the reference range (2.1-4.4pg/ml). Studies have reported that there is inconsistency in the thyroid functions in metabolic syndrome. The rise in TSH with normal T3 and T4 is mostly reported [20] and also the rise in TSH with alteration in T3 without any effect on T4[21] and increased thyroid hormone levels also have been reported in metabolic syndrome and

this supports our study as most of the patients with metabolic syndrome have increased FT3 values. However, FT4 value noted was 1.43743 ± 0.280609, which was within normal range 0.8-2.7ng/dl substantiating that the patients are in euthyroid state.

In our study, the uric acid value was found to be 4.828 ± 1.4841 in euthyroid patients of metabolic syndrome.

The correlation between TSH and eGFR (r=0.156) is accessed in this study and there is a positive correlation between them and the correlation is stronger than the correlation between triglycerides, HDL, total cholesterol, FT4 and eGFR. Another cross-sectional study conducted in Norway, reported that high TSH levels, within the euthyroid range, were associated with decreased eGFR and higher prevalence of CKD[22.]

There is a positive correlation between FT3 and eGFR (r=0.158) observed in euthyroid cases of metabolic syndrome with eGFR > 40 ml/ min/1.73 m2 and the correlation is not significant. But there is no relationship between FT4 and eGFR (r=-0.122) in euthyroid patients of metabolic syndrome. In a study significant relationship was found for FT3 and three MetS components in men, and all five components in women[2]. Studies reported that FT3 levels were positively correlated with eGFR and negatively correlated with serum creatinine levels. FT3 levels was reported to reduce as the severity of renal damage increased [24]. Low-normal levels of FT3 in euthyroid individuals from South Korea were associated with an increased risk of chronic kidney disease in a large cohort study.

In this study there is no correlation between eGFR, and HDL (r=-0.047), total cholesterol (r=-0.064), and triglycerides (r=0.033). Chen, J et al. reported that low HDL cholesterol and high triglyceride levels are associated with an increased risk for chronic kidney disease and microalbuminuria[6]. TG level was found to be negatively associated with the eGFR following multivariable adjustment [25]. H. Keskin et al. reported that the increased HDL was positively correlated with eGFR in the whole group[1].

Several studies have reported a negative correlation between high serum uric acid level and renal function. Similar to the previous studies, in our study, there is a significant negative correlation between serum uric acid level (r=-0.416) and eGFR in our patient group. Uric acid which is an inflammatory marker, is shown to have negative effects on renal function, and metabolic syndrome development through several pathways which includes endothelial dysfunction .The negative effect of high serum uric acid level on individuals with normal renal function (eGFR >40 and/or >60 ml/min/1.73 m2) has been demonstrated by both studies and meta-analyses [19] and this effect of uric acid has been independent of age, gender, BMI, Hypertension. Although high uric acid levels could be due to impaired uric acid clearance in CKD, it may be implicated in the development and progression of chronic kidney disease.

The multiple regression between eGFR and TSH with other variables is found to be significant ($p<0.005$). Multiple linear regression is conducted to determine the relationship between eGFR and various potential predictors and we found that there is a positive relationship of uric acid (b=-0.408) and eGFR, and the relationship is found significant ($p<0.05$). While the influence of other variables viz., Triglyceride (b=0.034), HDL (b=-0.055), FT3 (b=0.148), TSH (b=0.145), total Cholesterol (b=-0.083), and FT4 (b=-0.109) on eGFR is not significant (p not less than 0.05).

In our study, there is a significant negative correlation between serum uric acid level (r=-0.416) and eGFR in euthyroid metabolic syndrome patients. Therefore an increase in uric acid levels in euthyroid patients of metabolic syndrome may implicate that the individual is progressing towards CKD. This observation in euthyroid metabolic syndrome patients should be substantiated with further studies. In this study there is a positive correlation between FT3 and eGFR (r=0.158) observed in euthyroid cases of metabolic syndrome and there is no relationship between FT4 and eGFR (r=-0.122). Renal dysfunction is associated with various alterations in the thyroid hormone metabolism, release and action. More comprehensive and multicentric studies should be performed in patients with MetS to determine the association of FT3, FT4 in metabolic syndrome patients. Our results report that there is a positive association between TSH values and eGFR levels and there is a statistically significant negative association between uric acid and eGFR levels in euthyroid cases with metabolic syndrome.

CONCLUSION

This study was undertaken to evaluate the relationship between TSH values and eGFR levels in euthyroid cases with metabolic syndrome. In this study there is a positive correlation observed between TSH values and eGFR levels in euthyroid cases with metabolic syndrome. There is also a significant negative correlation between uric acid values and eGFR levels in euthyroid cases with metabolic syndrome. This negative correlation between uric acid values and eGFR levels may be used to identify the metabolic syndrome patients progressing towards CKD by monitoring the uric acid levels.

Limitations

- In this study we chose the eGFR rather than the measured GFR, which is a calculated value.
- This study was a single-center study, and there is regional homogeneity of the population visiting the Hospital. The data obtained does not reflect the general population.

REFERENCES

[1] Keskin H, Cadirci K, Gungor K, et al. Association between TSH Values and GFR Levels in Euthyroid Cases with Metabolic Syndrome. Int J Endocrinol. 2021;2021:8891972.

[2] Thomas G, Sehgal AR, Kashyap SR, et al. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2011;6(10):2364-2373.

[3] McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. Clin Dermatol. 2018 Jan-Feb;36(1):14-20

[4] Swarup S, Goyal A, Grigorova Y, et al. Metabolic Syndrome. [Updated 2021 Oct 30]. In:StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.

[5] Fahed G, Aoun L, Bou Zerdan M, et al. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. Int J Mol Sci. 2022 Jan 12;23(2):786.

[6] Chen, J. The Metabolic Syndrome and Chronic Kidney Disease in U.S. Adults. Annals of Internal Medicine, 2004;140(3):167.

[7] Prasad GV. Metabolic syndrome and chronic kidney disease: Current status and future directions. World J Nephrol. 2014;3(4):210-219.

[8] Inker LA, Heerspink HJL, Tighiouart H, et al. GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Meta-Analysis of Treatment Effects of Randomized Controlled Trials. J Am Soc Nephrol. 2019 Sep;30(9):1735-1745.

[9] Chang YC, Hua SC, Chang CH, et al. High TSH Level within Normal Range Is Associated with Obesity, Dyslipidemia, Hypertension, Inflammation, Hypercoagulability, and the Metabolic Syndrome: A Novel Cardiometabolic Marker. J Clin Med. 2019;8(6):817.

[10] Giovanni DP, Francesco G, Ritanna B, et al. Independent Influence of Insulin, Catecholamines, and Thyroid Hormones on Metabolic Syndrome. Obesity 2008; 16(11):2405-2411.

[11] Villabona C, Sahun M, Roca M, et al. Blood volumes and renal function in overt and subclinical primary hypothyroidism. Am J Med Sci. 1999;318:277-280.

[12] Heima, N. E., Eekhoff, E. M. W., Oosterwerff, M. M., Thyroid function and the metabolic syndrome in older persons: a population-based study. European Journal of Endocrinology, 2013. 168(1), 59-65.

[13] Zhang Y, Chang Y, Ryu S, et al. Thyroid hormone levels and incident chronic kidney disease in euthyroid individuals: the Kangbuk Samsung Health Study. Int J Epidemiol. 2014; 43:1624-1632.

[14] Sun, M.-T., Hsiao, F.-C., et al. Thyrotropin as an Independent Factor of Renal Function and Chronic Kidney Disease in Normoglycemic Euthyroid Adults. Endocrine Research, 2012 37(3), 110–116.

[15] Yanli Li, Min Yi, Xiaoyi Deng, et al. Evaluation of the Thyroid Characteristics and Correlated Factors in Hospitalized Patients with Newly Diagnosed Type 2 Diabetes. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 15, pages 2022 873-884.

[16] Sanchez-Lozada LG, Tapia E, Jimenez A, et al. Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats. Am J Physiol Renal Physiol. 2007;292:F423–F429.

[17] Chade AR, Hall JE. Role of the Renal Microcirculation in Progression of Chronic Kidney Injury in Obesity. American journal of nephrology. 2016;44:354–367.

[18] Zhang X, Lerman LO. The metabolic syndrome and chronic kidney disease. Translational Res. 2017 May;183:14-25

[19] Jalal D. I., Chonchol M., Chen W., et al. Uric acid as a target of therapy in CKD. American Journal of Kidney Diseases. 2013;**61**(1):134–146.
[20] Bastemir M, Akin F, Alkis E, et al. Obesity is associated with increased serum TSH level, independent of thyroid function. Swiss Med wkly. 2007;137:431–4.
[21] Kiortsis DN, Durack I, Turpin G. Effects of a low-calorie diet on resting metabolic rate and serum triiodothyronine levels in obese children. Eur J Pediatr. 1999;158:446–50.
[22] Asvold BO, Bjøro T, Vatten LJ. Association of thyroid function with estimated glomerular filtration rate in a population-based study: the HUNT study. Eur J Endocrinol. 2011; 164: 101-105.
[23] Wolffenbuttel, B.H.R., Wouters, et al. Thyroid function and metabolic syndrome in the population-based LifeLines cohort study. BMC Endocr Disord **17**, 65 (2017).
[24] Mehta HJ, Joseph LJ, Desai KB, et al. Total and free thyroid hormone levels in chronic renal failure. J Postgrad Med. 1991 Apr;37(2):79-83.
[25] Hu W, Wu XJ, Ni YJ, et al. Metabolic syndrome is independently associated with a mildly reduced estimated glomerular filtration rate: a cross-sectional study. BMC Nephrol. 2017Jun13;18(1):192.