DOI: 10.7860/JCDR/2019/37795.12898

Original Article

Biochemistry Section

Role of Gamma Glutamyl Transferase in the Diagnosis of Metabolic Syndrome in Patients with Hypothyroidism

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ABSTRACT

Introduction: Hypothyroidism is the most prevalent thyroid disorder in India that affects one in ten adults. Gamma Glutamyl Transferase (GGT) is an ectopic enzyme associated with oxidative stress in various diseased conditions. Prior research suggests that increased levels of GGT are associated with Metabolic Syndrome (MetS) in hypothyroidism.

Aim: To study the prevalence of MetS in patients with hypothyroidism and to correlate serum GGT levels with the components of MetS.

Materials and Methods: The case-control study was conducted on 62 clinically diagnosed hypothyroidism patients (cases) and 63 clinically proven healthy subjects (controls). All these subjects were screened for metabolic syndrome based on the NCEP ATP III (National Cholesterol Education Programme Adult Treatment Panel III) guidelines. Waist circumference, blood pressure, serum Fasting Blood Sugar (FBS), Urea, Creatinine, T3, T4, Thyroid Stimulating Hormone (TSH), Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C) and GGT were measured. Data was expressed as mean±SD and analysed using Independent Student t-test. The p-value <0.05 was considered as statistically significant.

Results: Waist circumference, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), FBS, TC, Triglycerides TG, LDL-C, GGT and TSH were significantly increased in hypothyroid cases when compared to the controls. HDL-C was significantly decreased in hypothyroid cases. Significant positive correlation was observed between GGT and TSH (r=0.57, p=0.004) in hypothyroid cases with MetS. Significant inverse correlation was observed between GGT and HDL-C (r=-0.25, p=0.04) in hypothyroid cases.

Conclusion: In this study, 38% of hypothyroid patients had MetS. Serum GGT is found to be elevated in hypothyroid cases and associated with components of MetS. Hence GGT can be used as an additional diagnostic marker to assess the MetS in hypothyroidism.

Keywords: High density lipoprotein, Low density lipoprotein, Thyroid stimulating hormone

INTRODUCTION

Thyroid disorders are among the most prevalent endocrine disorders worldwide. Globally, 300 million people are suffering from thyroid disorders. In India, 42 million people are affected by thyroid disorders [1]. Hypothyroidism, is the most common of thyroid disorders in India, affecting one in ten adults with prevalence ranging from 7.33-10.2%. Thyroid dysfunction is more prevalent among women compared to men [2-4]. One in every eight women during their lifetime is at risk of developing thyroid disorder. Though the exact mechanism is not known, it is believed to be associated with oestrogen and progesterone. Iodine intake, sex, age, ethnic and geographical factors influences the incidence of thyroid disorders. Hypothyroidism is known to be associated with MetS due to increased LDL, TG, BP and plasma glucose, which in turn contributes to atherogenic dyslipidemia and leads on to an increased cardiovascular risk [5].

GGT is involved in metabolism of an intracellular antioxidant glutathione. Oxidative stress is one of the pathophysiology involved in several obesity related disorders such as MetS, hypertension, type 2 diabetes mellitus and dyslipidemia [6]. Epidemiological studies suggest that, GGT is an independent risk factor for the mortality and morbidity for cardiovascular diseases [7,8]. Additional prospective studies reported that baseline serum GGT concentration is an independent risk factor for the development of Coronary Artery Disease (CAD), diabetes mellitus, stroke and hypertension [9,10]. Recent research is focused on identification and evaluation of biochemical markers that can predict early onset of MetS and subsequently intervene by means of lifestyle changes and drug therapy to reduce cardiovascular morbidity and mortality.

Based on the available literature, we hypothesised that high GGT levels, are associated with MetS in hypothyroidism and hence can have a predictive value in the diagnosis of MetS in hypothyroidism. To test this hypothesis, lipid profile (TC, TG, HDL-C and LDL-C), fasting blood glucose levels, GGT, TSH, blood pressure and waist circumference of subjects under study were analysed with following objectives to study the prevalence of metabolic syndrome in patients with hypothyroidism and to correlate serum GGT levels with the components of metabolic syndrome.

MATERIALS AND METHODS

The present case-control study included 125 subjects in the age group between 22-55 years. Clinically diagnosed 62 hypothyroidism patients attending Medicine department, outpatient and inpatient, from September 2015 to December 2015 at RL Jalappa hospital and Research centre Kolar, Karnataka, India, were recruited in the study [10]. After a thorough clinical and biochemical examination, 63 age and gender-matched healthy individuals accompanying the patients and individuals from medical college staffs were enrolled as control in the study. Sample size was calculated considering mean difference of GGT as 34.42 mg/dL at 95% power and 80% confidence interval, minimum of 7 samples to be included in each group.

Both newly diagnosed patients and patients on treatment from 1-5 years were included. These subjects were screened for MetS based on Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP-III) [11]. Subjects fulfilling three or more National Cholesterol Education Program (NCEP) ATP III criteria were included under MetS

I. Waist circumference >102 cm in men and >88 cm in women
II. Blood pressure ≥130/≥85 mmHg
III. Triglycerides ≥150 mg/dL
IV. HDL cholesterol <40 mg/dL in males and <50 mg/dL in females
V. Fasting glucose ≥110 mg/dL

Patients with acute or chronic hepatitis, chronic alcoholism, malignant disease, severe renal insufficiency, cirrhosis, pregnancy, patients with history of cardiovascular disease, patients who are on hypolipidemic drugs and oral contraceptives were excluded from the study.

The study protocol was approved by the Institutional Ethical Committee (No. DMC/KLR/IC/41/2015-16 dated 04.09.2015). Voluntary written informed consent in their understandable language was obtained from all the subjects under study.

All subjects enrolled in the study underwent detailed clinical examination including measurements of height, weight, Waist Circumference (WC), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). WC was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch resistant tape (Intra individual Measurement Error±1.31 cm) [12]. Blood pressure was measured from the left arm in the sitting position placing BP apparatus (Omron HEM-8712) at the level of the heart.

After explaining the procedure to the subjects under study, 2 mL of fasting venous blood was drawn from all patients under aseptic precautions in red vaccutainer tubes. Samples were incubated at room temperature for 20 minutes and then centrifuged at 3000 rpm for 4 minutes. Serum was then used for the estimation of biochemical parameters using Johnson and Johnson Vitros 250 dry chemistry auto-analyser. The blood Glucose estimation was done by Glucose Oxidase Peroxidase method (GOD-POD), Urea by Urease method, Creatinine by enzymatic kinetic method, Total Cholesterol by cholesterol oxidase method, TG by Enzymatic colorimetric test- GPO PAP, HDL-C by Direct Enzymatic colorimetric, LDL-C calculated by Friedwald's formula [13-15]. GGT was estimated by G-glutamyl-p-nitroanilide method [16]. TSH estimated by chemiluminescence method using vitros Eci [17].

STATISTICAL ANALYSIS

Statistical analysis was carried out by the Independent Student t-test by using the Statistical Package for the Social Sciences (SPSS) version 20.0. Data were expressed as mean±SD, p-value <0.05 was considered as statistically significant and pearson correlation was used to determine correlation between GGT and TSH levels.

RESULTS

Study included 62 clinically diagnosed cases of hypothyroidism. The mean age group of cases was 37.4±14.3 years and controls 39.9±12.6 years. Among the cases, 55 (88.7 %) were females and 7 (11.3%) were males. A 38% of the hypothyroid cases had MetS, of which 50.7% of the cases had increased waist circumference, 22% had increased BP, 19% had impaired fasting blood glucose, 43% had increased TG levels and 59 % had decreased HDL-C levels. The baseline characteristics and biochemical parameters of the controls and cases (hypothyroid patients) were compared. Mean values of WC, SBP, DBP, FBS, TC, TG, LDL-C, GGT and TSH levels were increased in cases when compared to controls except for HDL-C [Table/Fig-1]. These biochemical parameters were studied for the cases with and without MetS [Table/Fig-2]. WC, FBS, TG, LDL-C and GGT were significantly elevated and HDL-C statistically decreased in hypothyroid patients with MetS when compared to the hypothyroid patients without MetS. Significant inverse correlation (r=-0.25, p=0.04) was observed between GGT and HDL levels. However, there was no significant correlation observed with respect to other components of MetS [Table/Fig-3].

Parameters	Controls (n=63)	Cases (n=62)	p-value
WC (cm)	85.0±7.2	88.7±11.9	0.04*
SBP (mm of Hg)	112±8.0	122±10.0	0.00**
DBP (mm of Hg)	80±10.0	90±12.0	0.00**
FBG (mg/dL)	79.9±13.3	94.5±27.8	0.00**
Serum Urea (mg/dL)	23.03±7.2	25.4±7.3	0.08
Serum Creatinine (mg/dL)	0.72±0.17	0.74±0.17	0.45
Serum TC (mg/dL)	147.6±29.4	172.8±43.1	0.03*
Serum TG (mg/dL)	114.6±36.7	155.15±44.8	0.00**
Serum HDL-C (mg/dL)	47.4±9.4	42.9±10.3	0.01*
Serum LDL-C (mg/dL)	88.2±22. 3	94.3±33.2	0.23
Serum GGT (IU/L)	15.3±9.9	20.6±11.5	0.00**
Serum TSH (µLU/mL)	6.99±3.4	16±9.5	0.03*

[Table/Fig-1]: Baseline characteristics and biochemical parameters among controls and hypothyroid cases.
WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; GGT: Gamma glutamyl transferase; TSH: Thyroid stimulating hormone
Data expressed as Mean±SD. Independent Student t-test was used and p-value p<0.05, *Significant, p<0.001 **Highly Significant is considered

Parameters	Hypothyroid with Met S (n=23)	Hypothyroid without Met S (n=40)	p-value
WC (cm)	97.3±10.8	83.9±9.5	0.00**
FBG (mg/dL)	106.0±39.8	88.3±14.4	0.01*
Serum Urea (mg/dL)	24.1±8.6	26.0±6.3	0.36
Serum Creatinine (mg/dL)	0.77±0.18	0.72±0.16	0.29
Serum TC (mg/dL)	183.5±43.5	169.2±45.1	0.22
Serum TG (mg/dL)	228.5±112.8	124±47.5	0.00**
Serum HDL (mg/dL)	36.6±6.0	43.8±7.4	0.00**
Serum LDL (mg/dL)	101.0±33.7	91.6±32.0	0.00**
Serum GGT (IU/L)	20.4±8.08	16.6±5.9	0.04*
Serum TSH (µLU/mL)	14.3±5.08	11.31±2.9	0.61

[Table/Fig-2]: Baseline characteristics and biochemical parameters among hypothyroidism cases with and without Metabolic Syndrome (MetS).
WC: Waist circumference; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; GGT: Gamma glutamyl transferase; TSH: Thyroid stimulating hormone
Data expressed as Mean±SD. Independent Student t-test was used and p-value p<0.05, *Significant, p<0.001 **Highly Significant is considered

Positive correlation (r=0.57, p=0.004) was observed between GGT with TSH in patients with MetS when compared to patients without MetS [Table/Fig-4].

DISCUSSION

Thyroid hormones are known to play an important role in regulating the synthesis, metabolism and mobilisation of lipids. Numerous studies reported an association of thyroid dysfunction and MetS [18,19]. MetS is characterised by central obesity, hypertriglyceridemia, low HDL-C, hyperglycemia and hypertension. The MetS is known to be associated with high risk of Cardiovascular Disease (CVD) and cerebrovascular disease [19].

In the present study, 38% of the hypothyroid cases had MetS. A study conducted by Punia VPS reported 55% prevalence of MetS in hypothyroid cases in urban population [20]. Bhaddur Thapa B et al., reported prevalence of MetS in sub-clinical hypothyroidism as 44% whereas 62.0% in overt hypothyroidism. Overall prevalence of Met S in hypothyroid patients was 37.6% which is similar to our findings [19].

In our study, waist circumference was significantly increased in hypothyroid cases when compared to controls and was significantly higher in patients with MetS when compared to patients without MetS. Systolic and diastolic blood pressure was significantly increased in hypothyroid cases when compared to controls and

		WC	FBS	TC	TG	HDL	LDL	GGT
WC	Pearson correlation		0.16	0.19	0.29*	-0.29*	0.07	0.23
	p-value		0.19	0.12	0.01	0.02	0.56	0.06
FBS	Pearson correlation	0.16		0.10	0.06	-0.03	-0.03	0.07
	p-value	0.19		0.41	0.59	0.78	0.80	0.55
TC	Pearson correlation	0.19	0.10		0.33**	0.06	0.83**	0.13
	p-value	0.11	0.41		0.00	0.61	0.00	0.30
TG	Pearson correlation	0.29*	0.06	0.33**		-0.35**	-0.08	0.20
	p-value	0.01	0.59	0.00		0.00	0.53	0.11
HDL	Pearson correlation	-0.29*	-0.03	0.06	-0.35**		0.16	-0.25*
	p-value	0.02	0.78	0.61	0.00		0.19	0.04
LDL	Pearson correlation	0.07	-0.03	0.83**	-0.08	0.16		0.09
	p-value	0.56	0.80	0.00	0.53	0.19		0.44
GGT	Pearson correlation	0.23	0.07	0.13	0.20	-0.25*	0.09	
	p-value	0.06	0.55	0.30	0.11	0.04	0.44	

[Table/Fig-3]: Correlation of GGT with the components of metabolic syndrome (MetS) in patients with hypothyroidism.
*Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level (2-tailed)
WC: Waist circumference; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; GGT: Gamma glutamyl transferase; TSH: Thyroid stimulating hormone. Pearsons correlation Test was used and p<0.001 is considered as highly significant and p<0.05 is considered as significant

		Hypothyroid with MetS (n=22)	Hypothyroid without MetS (n=40)
		TSH	
GGT	Pearson correlation (r-value)	0.57	0.6
	p-value	0.004*	0.96

[Table/Fig-4]: Correlation of GGT with TSH in hypothyroid patients with and without Metabolic Syndrome (Mets).
GGT: Gamma glutamyl transferase; TSH: Thyroid stimulating hormone. Pearson correlation Test was used and p<0.001 is considered as highly significant and p<0.05 is considered as significant

22% hypothyroid cases had increased BP. These observations suggest that elevated blood pressure is an important contributing factor for metabolic syndrome. Haemodynamic alterations in hypothyroidism causes narrowing of pulse pressure, prolongation of circulatory time and reduced blood flow to the tissues. Increased systemic vascular resistance results in hypertension. Our observations are similar to studies conducted by Pandey R et al., and Moura Souza A et al., that showed positive correlation between serum TSH, BMI and hypertension [21,22].

Hypothyroid cases showed increased FBS, TC, TG and decreased HDL levels. Similar results were observed in hypothyroid cases with MetS when compared to non-MetS patients. This observation is in accordance with studies conducted by McDermott MT et al., and Duntas LH et al., [23,24]. Thyroid hormones play an important role in the regulation of energy balance, metabolism of glucose, and lipids. Generally, more than 60% of hypothyroid patients are obese and have a low resting metabolic rate and energy metabolism. In hypothyroidism, synthesis and degradation of lipids are depressed; resulting in lipid accumulation, especially LDL cholesterol and triglycerides. In hypothyroidism, the elevated serum cholesterol levels are accompanied by increased levels of serum phospholipids, serum triglycerides and LDL cholesterol. The activity of cholesterol ester transfer protein is significantly reduced which leads to lowered HDL cholesterol levels [25,26].

Our study showed increased levels of GGT in hypothyroid cases. Though GGT is within the normal reference range, it is elevated significantly in MetS when compared to non MetS. These observations were in accordance with the studies done by Mohammad Saleem MMN et al., and Ulla L et al., [27,28]. In a cross-sectional study by Kasapoglu B et al., high baseline GGT concentrations were found to be associated with MetS. Increased GGT levels were also positively correlated with presence of cardiovascular diseases in MetS group when compared to low GGT group [29]. MetS is associated with Non-Alcoholic Fatty Liver Disease [NAFLD] which is characterised by fatty infiltration with necroinflammatory change which may progresses to variable degrees of fibrosis. These elevated GGT levels could be attributed to NAFLD [28].

GGT is an ectopic enzyme which maintains the intracellular concentrations of antioxidant glutathione. Elevated GGT in MetS is linked to oxidative stress pathway [30]. Wei D et al., hypothesised that GGT and ferritin are elevated in MetS and substantiated the role of these markers in lipid peroxidation and which subsequently can lead to insulin resistance and MetS [31]. A significant positive correlation of GGT levels with waist circumference, TSH and significant negative correlation with HDL. However, the exact mechanism responsible for this association remains debatable; multiple probable mechanisms have been proposed on the action of serum GGT in increasing cardiovascular risk. Higher GGT levels could be attributed to oxidative stress, along with hepatic insulin resistance and subclinical inflammation [32]. Hence GGT can be used as an indicator of onset of MetS in hypothyroid cases. This may help in prevention of cardiovascular risks and other complications related to MetS.

LIMITATION

Estimation of FT3 and FT4 was not done. Iodine nutrition status in the patients was not assessed. Large prospective studies are needed.

CONCLUSION

The present study showed a positive correlation of MetS with hypothyroidism. Serum GGT is elevated in hypothyroid cases as well as in hypothyroid patients having MetS. Since, serum GGT is an independent risk factor for cardiovascular diseases, estimation of serum GGT can be considered as a screening test which would help to identify the risk of MetS and cardio-metabolic risk factors in hypothyroidism.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jul 07, 2018**
Date of Peer Review: **Aug 14, 2018**
Date of Acceptance: **Apr 20, 2019**
Date of Publishing: **Jun 01, 2019**