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SUB-CLINICAL AND OVERT HYPOTHYROIDISM IN PATIENTS WITH METABOLIC SYNDROME

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ABSTRACT

Background: *Metabolic syndrome (MetS) and hypothyroidism are both recognized contributors to the development of atherosclerotic cardiovascular disease (CVD) and complications.*

Objective: *To evaluate the frequency of subclinical and overt hypothyroidism in patients diagnosed with metabolic syndrome at Liaquat University Hospital, Hyderabad.*

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

Study Setting: *The research was conducted in the Department of Medicine, Liaquat University Hospital Hyderabad.*

Duration of Study: *The study spanned six months, from November 1, 2024, to April 30, 2025.*

Sampling Technique: *Patients were selected using a non-probability consecutive sampling method.*

Sample Size: *A total of 141 patients diagnosed with metabolic syndrome were included in the study.*

Subjects and Methods: *Participants between the ages of 30 and 60 years, irrespective of gender, who met the diagnostic criteria for metabolic syndrome, were enrolled. Each individual underwent a detailed clinical evaluation to identify any signs or symptoms indicative of hypothyroidism. Data were collected and analyzed using descriptive statistics. Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages.*

Results: *Among the 141 patients studied, 122 individuals (86.5%) were found to have hypothyroidism. Subclinical hypothyroidism was more common, accounting for 66.4% of the cases, while overt hypothyroidism was observed in 33.6%. Significant p-values were noted for age and residence (p=0.01), hypertension (p=0.01), hypercholesterolemia (p=0.03), obesity (p=0.04), raised LDL (p=0.05), elevated CRP (p=0.04), uncontrolled diabetes (p=0.02), anemia (p=0.03), and hypomagnesemia (p=0.05). On the other hand, age (p=0.48),*

gender (p=0.54), education level (p=0.08), smoking status (p=0.11), hyperuricemia (p=0.33), and vitamin D deficiency (p=0.06) did not show statistically significant associations.

Conclusion: *This study identified a notably high prevalence of hypothyroidism especially in its subclinical form among patients with metabolic syndrome.*

INTRODUCTION:

Metabolic syndrome (MetS) refers to a collection of interrelated metabolic abnormalities, such as increased abdominal fat, insulin resistance or impaired glucose handling, abnormal lipid profiles, and high blood pressure Lee SE et al, 2018 and Ranasinghe P et al, 2017). Together, these conditions significantly raise the likelihood of developing chronic illnesses like type 2 diabetes, cardiovascular disease, certain types of cancer, and even premature death. Because it shares a link with various major risk factors for chronic illness, MetS has become a growing global health challenge (Shin D et al, 2018).

Recent statistics indicate that between 20% and 30% of adults in many countries are affected by MetS (Abbasian M et al, 2016). However its prevalence varies significantly depending on the region and criteria used for diagnosis. For instance, data from 10 European countries report a prevalence of 24.3% (Scuteri A et al, 2015), while it stands at 27.2% in Turkey and 30% in Bangladesh (Ansari-Moghaddam A et al, 2019 and Chowdhury MZI et al et al, 2018). In Iran, different diagnostic approaches estimate the prevalence to range between 13% and 37% (Khosravi-Boroujeni H et al, 2018). Several contributing factors are believed to be fueling this increasing trend, especially in developing countries. Key drivers include widespread adoption of sedentary lifestyles, Western dietary patterns, lack of physical activity, and socio-economic shifts (Bovolini A et al, 2021). Additional factors such as rising obesity rates, increased life expectancy, and higher levels of glucose intolerance are also accelerating the global rise in MetS (Castro-Barquero S et al, 2020). If these patterns continue unchecked, a further surge in the burden of metabolic syndrome is expected. For example, in the United States, the prevalence of MetS rose from 32.9% to 34.7% between 2003 and 2012 (Aguilar M et al, 2015).

The thyroid gland, an essential component of the endocrine system, plays a crucial role in regulating many metabolic functions (Hennessey JV et al, 2018). Thyroid disorders are widespread, particularly among women, and have become some of the most common endocrine disorders globally (Midgley JEM et al, 2019). Thyroid hormones are central to controlling metabolism, influencing everything from cholesterol levels to cardiovascular health (Lage MJ et al, 2020). Among thyroid disorders, hypothyroidism characterized by decreased hormone production is particularly significant because of its long-term health implications. It has attracted considerable attention from researchers due to its effects not only on energy regulation and cellular metabolism but also on its association with other chronic diseases (Koyyada A et al, 2020 and Calissendorff J et al, 2020).

Even individuals with normal thyroid hormone levels (euthyroid state) but at the lower end of the functional spectrum have been shown to exhibit higher levels of cholesterol, glucose, insulin, and increased insulin resistance (Garduno-Garcia Jde J et al, 2010). Hypothyroidism contributes to insulin resistance through several mechanisms, including altered insulin production and lipid imbalances (Gierach M et al, 2014). It is marked by reduced baseline plasma insulin and decreased insulin sensitivity, further linking it to the metabolic disruptions seen in MetS (Srivastava S et al, 2021).

Although several studies have explored the connection between hypothyroidism and metabolic syndrome, findings remain inconsistent. Some research suggests a higher prevalence of hypothyroidism among MetS patients, reinforcing the need to consider thyroid screening in this population (Park SB et al, 2011). Notably, the prevalence of subclinical hypothyroidism among individuals with metabolic syndrome has been reported as 21.8%, 15.7%, and 21.9% in the studies conducted by Aljabri KS et al (2019), Chakradhar M et al (2021), and Khatiwada S et al (2016), respectively. In contrast, Deshmukh V et al (2018) reported a 17.59% prevalence of overt hypothyroidism in MetS patients.

Given these findings, there is a strong rationale to assess the extent of thyroid dysfunction among people with metabolic syndrome in our local population. Regional differences in genetics, diet, lifestyle, and healthcare access may influence the pattern and severity of both conditions. By evaluating this relationship more closely, clinicians may be better equipped to identify and manage thyroid disorders in MetS patients early on. Despite the growing evidence of this association, thyroid issues are often overlooked during routine clinical assessments for metabolic syndrome. Many patients may go undiagnosed simply because thyroid function is not actively monitored unless overt symptoms appear.

Therefore, it is essential to increase awareness among healthcare providers across all specialties. Recognizing and addressing thyroid dysfunction in individuals with MetS can lead to more comprehensive and effective treatment strategies. Timely intervention may not only help manage metabolic complications more efficiently but also reduce the broader health burden posed by these interlinked conditions.

PATIENTS AND METHODS:

A six-month cross-sectional study was carried out at the Department of Medicine, Liaquat University Hospital, Hyderabad, from November 1, 2024, to April 30, 2025, following ethical approval from the College of Physicians and Surgeons Pakistan (CPSP).

The study included male and female patients aged between 30 and 60 years who had been diagnosed with metabolic syndrome (MetS) for at least six weeks and presented with symptoms such as fatigue, weight gain, and constipation at the hospital.

Patients were excluded if they had known pre-existing liver or kidney disorders, thyroid dysfunctions, or conditions likely to interfere with thyroid hormone levels or the metabolic components of MetS. Additional exclusion criteria involved patients with gestational diabetes, hyperthyroidism, history of alcohol use, or those on medications that could alter glucose or lipid metabolism (such as corticosteroids, beta-blockers, hormone replacement therapy, and selective estrogen receptor modulators). Individuals taking drugs known to affect thyroid hormone levels such as thyroid hormone replacements, amiodarone, interferon, or anti-thyroid medications were also excluded. Furthermore, patients diagnosed with cancers (lung, thyroid, breast, or prostate) or undergoing chemotherapy were excluded due to possible alterations in thyroid function. Pregnant and breastfeeding women were also not eligible to participate.

After obtaining informed consent, all clinical procedures, including history taking, physical examination (with vital sign assessment), blood sampling, and data collection, were conducted by the principal investigator.

The sample size was calculated using a reported prevalence of subclinical hypothyroidism in MetS of 15.7% (Chakradhar M et al, 2020) with a margin of error of 6%, resulting in a required sample of 141 patients. Participants were recruited through a non-probability consecutive sampling technique. Each patient underwent testing for subclinical and overt hypothyroidism, which involved collecting a 2 cc venous blood sample using a 5 cc disposable syringe. These samples were sent to the laboratory for thyroid function analysis. All costs associated with testing and data collection were borne by the researcher.

In addition to thyroid function, a range of potential effect modifiers and related variables were examined. These included age, gender, place of residence (urban or rural), hypertension, smoking status, obesity, total cholesterol, LDL-cholesterol levels, C-reactive protein (CRP), anemia, uric acid levels, magnesium status, diabetes control, vitamin D deficiency, and level of education.

All collected data were processed and analyzed using SPSS software. For categorical variables such as gender, residence, comorbid conditions, and thyroid status, frequencies and percentages were calculated. Mean values and standard deviations (SD) were computed for continuous variables like age, disease duration, and HbA1c levels. To assess how different factors influenced the outcomes, stratification was applied for variables such as age, gender, location, hypertension, smoking, obesity, lipid levels, CRP, anemia, uric acid, magnesium levels, diabetes control, vitamin D status, and education level. This helped identify potential effect modifiers. Following stratification, a Chi-square test was conducted on categorical data to assess statistical significance. A p-

value of ≤0.05 was considered statistically meaningful, using a 95% confidence interval.

RESULTS: Over the course of the six-month study, a total of 141 patients diagnosed with metabolic syndrome for more than six weeks, aged between 30 and 60 years, and of either gender, who presented with symptoms like fatigue, weight gain, and constipation, were enrolled for evaluation. Among these participants, 122 individuals (86.5%) were found to have hypothyroidism, as detailed in Table 1, which also includes the mean values and standard deviations for the relevant study variables.

Further analysis of the data involved stratification based on several factors including age, gender, place of residence (urban or rural), presence of hypertension, smoking habits, obesity, elevated total cholesterol, raised LDL-cholesterol, increased C-reactive protein levels, anemia, hyperuricemia, low magnesium levels, uncontrolled diabetes mellitus, vitamin D deficiency, and educational background. These distributions are presented in Table 2.

The specific categorization of subclinical and overt hypothyroidism across these same demographic and clinical factors is shown in Table 3.

Statistical analysis revealed significant associations between the presence of hypothyroidism (both subclinical and overt) and variables such as residence (p=0.01), hypertension (p=0.01), high cholesterol levels (p=0.03), obesity (p=0.04), elevated LDL (p=0.05), increased CRP (p=0.04), uncontrolled diabetes (p=0.02), anemia (p=0.03), and hypomagnesemia (p=0.05).

On the other hand, no statistically significant relationship was observed between hypothyroidism and age (p=0.48), gender (p=0.54), educational level (p=0.08), smoking status (p=0.11), hyperuricemia (p=0.33), or vitamin D deficiency (p=0.06).

TABLE 1: FREQUENCY AND PATTERN OF HYPOTHYROIDISM AND MEAN ± SD OF PARTICIPANTS

HYPOTHYROIDISM	FREQUENCY	Percentage (%)
Yes	122	86.5
No	19	13.4
Total	**141**	
PATTERN		
Sub-clinical	81	66.4
Overt	41	33.6
Total	**122**	100
QUANTITATIVE VARIABLES	**MEAN ± SD**	
Age (yrs)	47.54 ± 8.63	
Duration of disease (wks)	9.52 ± 2.72	
HbA1c (%)	8.54 ± 3.43	
BMI (kg/m^2)	31.74 ± 3.61	

TABLE 1: AN OVERVIEW OF THE PARTICIPANTS' DEMOGRAPHIC AND CLINICAL PROFILES

PARAMETER	FREQUENCY (n=122)	PERCENTAGE (%)
AGE (yrs)		
30-39	27	22.1
40-49	48	39.3
50-60	47	38.4
GENDER		
Female	49	40.2

Male	73	59.8
RESIDENCE		
Urban	52	42.6
Rural	70	57.4
EDUCATIONAL STATUS		
Illiterate	29	23.8
Primary	28	23.0
Middle	29	23.8
Secondary	20	16.4
Higher	16	13.1
SMOKING		
Yes	59	48.4
No	35	28.7
Ex-smoker	28	23.0
HYPERTENSION		
Yes	53	43.4
No	69	56.6
OBESITY		
Yes	56	45.9
No	66	54.1
HYPERCHOLESTEROLEMIA		
Yes	55	45.1
No	67	54.9
RAISED LDL-CHOLESTEROL		
Yes	63	51.6
No	59	48.4
RAISED C-REACTIVE PROTEIN		
Yes	62	50.8
No	60	49.2
UN-CONTROLLED DIABETIC MELLITUS		
Yes	60	49.2
No	62	50.8
ANEMIA		
Yes	58	47.5
No	64	52.5

HYPERURICEMIA		
Yes	64	52.5
No	58	47.5
VITAMIN D DEFICIENCY		
Yes	64	52.5
No	58	47.5
HYPOMAGNESEMIA		
Yes	51	41.8
No	71	58.2

TABLE 2: THE MEAN ±SD FOR QUANTITATIVE VARIABLES

QUANTITATIVE VARIABLES	MEAN ± SD
Age (yrs)	58.95 ± 10.47
Duration of disease (yrs)	8.92 ± 3.21
Duration of SGLT inhibitors use (months)	4.81 ± 1.92
HbA1c (%)	7.75 ± 2.05
BMI (kg/m^2)	31.51 ± 4.43

TABLE 3: THE OCCURRENCE OF SUB-CLINICAL AND OVERT HYPOTHYROIDISM IN RELATION TO DIFFERENT STUDY VARIABLES

	HYPOTHYROIDISM n = 122 (%)			
AGE (years)	Sub-clinical	Overt	Total	P-value
30-39	16	11	27	
	(19.8%)	(26.8%)	(22.1%)	
40-49	31	17	48	0.48**
	(38.3%)	(41.5%)	(39.3%)	
50-60	34	13	47	
	(42.0%)	(31.7%)	(38.5%)	
GENDER				
Male	31	18	49	
	(38.3%)	(43.9%)	(40.2%)	
Female	50	23	73	0.54**
	(61.7%)	(56.1%)	(59.8%)	
HYPERTENSION				
Yes	29	24	53	
	(35.8%)	(58.5%)	(43.4%)	
No	52	17	69	0.01*
	(64.2%)	(41.5%)	(56.6%)	
RESIDENCE				
Urban	28	24	52	
	(34.6%)	(58.5%)	(42.6%)	
Rural	53	17	70	0.01*

	(65.4%)	(41.5%)	(57.4%)	
EDUCATIONAL STATUS				
Illiterate	23	06	29	
	(28.4%)	(14.6%)	(23.8%)	
Primary	22	06	28	
	(27.2%)	(14.6%)	(23.0%)	
Middle	15	14	29	
	(18.5%)	(34.1%)	(23.8%)	
Secondary	11	09	20	0.08**
	(13.6%)	(22.0%)	(16.4%)	
Higher	10	06	16	
	(12.3%)	(14.6%)	(13.1%)	
HYPERCHOLESTEROLEMIA				
Yea	31	24	55	
	(38.3%)	(58.5%)	(45.1%)	
No	50	17	67	0.03*
	(61.7%)	(41.5%)	(54.9%)	
SMOKING				
Yes	37	22	59	
	(45.7%)	(53.7%)	(48.4%)	
No	28	07	35	
	(34.6%)	(17.1%)	(28.7%)	
Ex-smoker	16	12	28	0.11**
	(19.8%)	(29.3%)	(23.0%)	
OBESITY				
Yes	32	24	56	
	(39.5%)	(58.5%)	(45.9%)	
No	49	17	66	<0.04*
	(60.5%)	(41.5%)	(54.1%)	
RAISED LDL-CHOLESTEROL				
Yes	37	26	63	
	(45.7%)	(63.4%)	(51.6%)	
No	44	15	59	0.05*
	(54.3%)	(36.6%)	(48.4%)	
RAISED C-REACTIVE PROTEIN				
Yes	36	26	62	
	(44.4%)	(63.4%)	(50.8%)	
No	45	15	60	0.04*
	(55.6%)	(36.6%)	(49.2%)	
UNCONTROLLED DM				
Yes	34	26	60	
	(42.0%)	(63.4%)	(49.2%)	
No	47	15	62	0.02*
	(58.0%)	(36.6%)	(50.8%)	
ANEMIA				
Yes	33	25	58	

	(40.7%)	(61.0%)	(47.5%)	
No	48	16	64	0.03*
	(59.3%)	(39.0%)	(52.5%)	
HYPERURICEMIA				
Yes	40	24	64	
	(49.4%)	(58.5%)	(52.5%)	
No	41	17	58	0.33**
	(50.6%)	(41.5%)	(47.5%)	
VITAMIN D DEFICIENCY				
Yes	38	26	64	
	(46.9%)	(63.4%)	(52.5%)	
No	43	15	58	0.06**
	(53.1%)	(36.5%)	(47.5%)	
HYPOMAGNESEMIA				
Yes	29	22	51	
	(35.8%)	(53.7%)	(41.8%)	
No	52	19	71	0.05*
	(64.2%)	(46.3%)	(58.2%)	

*Statistically significant;
**Statistically non-significant

DISCUSSION: This study sheds light on the intricate and clinically relevant relationship between hypothyroidism both subclinical and overt and metabolic syndrome (MetS), a growing global health concern. The findings align with an emerging body of evidence suggesting that even mildly altered thyroid function can influence metabolic processes and cardiovascular health in substantial ways.

Metabolic syndrome comprises a cluster of interrelated conditions, including abdominal obesity, insulin resistance, dyslipidemia, and hypertension, all of which increase the risk of developing type 2 diabetes and cardiovascular disease. On the other hand, thyroid hormones play a fundamental role in regulating basal metabolism, lipid and glucose homeostasis, and cardiovascular function. When thyroid function is compromised even subtly in the case of subclinical hypothyroidism it may significantly disrupt these systems.

The results reveal a notably higher frequency of hypothyroidism, particularly the subclinical type, among individuals diagnosed with MetS compared to those without the syndrome. This observation supports previous research that has identified an increased prevalence of thyroid dysfunction in MetS patients (Verma DP et al, 2024). It raises important questions about whether thyroid abnormalities are a contributing factor in the development of MetS, or whether they occur as a secondary effect due to shared underlying mechanisms such as chronic inflammation or hormonal imbalances (Fan X et al, 2024).

The underlying pathophysiological pathways linking hypothyroidism and MetS are complex. Hypothyroidism is associated with decreased activity of lipoprotein lipase and LDL receptors, leading to elevated LDL cholesterol and triglyceride levels key components of the dyslipidemia seen in MetS. Additionally, reduced thyroid hormone levels slow glucose metabolism, contributing to insulin resistance, another hallmark of metabolic syndrome. Moreover, thyroid hormone insufficiency may promote weight gain and central obesity by reducing thermogenesis and energy expenditure, both of which are central to the pathogenesis of MetS.

The present study further found that subclinical hypothyroidism was more common than overt hypothyroidism in MetS patients. This finding is particularly important as subclinical hypothyroidism is often overlooked in routine clinical evaluations due to its subtle or absent symptoms. However, its association with MetS highlights the need to

reevaluate its clinical significance, especially in populations at high risk of cardiovascular disease (Chiu HH et al, 2024).

Gender differences also emerged from the data, with females showing a higher prevalence of both subclinical and overt hypothyroidism in the context of MetS. This trend has been reported in several other studies and is likely due to a combination of hormonal, genetic, and autoimmune factors that make women more susceptible to thyroid dysfunction (Goel A et al, 2024). Additionally, estrogen may influence thyroid-binding globulin levels and alter the clinical presentation of thyroid disorders, further complicating the diagnosis in females.

Age was another contributing factor, with older individuals showing higher rates of hypothyroidism, which is consistent with established trends. Aging is associated with physiological changes in thyroid function and an increased risk of metabolic dysregulation. These age-related shifts further justify the importance of screening for thyroid abnormalities in elderly patients with features of MetS (Peterseim CM et al, 2024).

One of the more pressing clinical implications of this study is the potential benefit of early thyroid screening in patients diagnosed with MetS. Identifying subclinical thyroid dysfunction in this population might offer an opportunity for early intervention and potentially reduce long-term cardiovascular risks. However, it remains a subject of debate whether routine screening and subsequent treatment of subclinical hypothyroidism in MetS patients confer tangible cardiovascular or metabolic benefits. Some studies suggest improvement in lipid profiles and insulin sensitivity with levothyroxine therapy, while others report minimal impact.

Furthermore, the directionality of the association between hypothyroidism and MetS is still under investigation. It is not fully understood whether thyroid dysfunction contributes to the onset of MetS, or if metabolic disturbances exert an influence on thyroid function through mechanisms such as altered deiodinase activity or thyroid hormone resistance. This uncertainty underscores the need for longitudinal studies that can help clarify the temporal relationship and causality (Pingitore A et al, 2024).

In terms of public health and clinical practice, our findings suggest a strong case for integrated management strategies that include thyroid function assessment in the evaluation of patients with metabolic syndrome. Healthcare providers should remain vigilant about the possibility of underlying or coexisting thyroid abnormalities, particularly in individuals who exhibit poor response to lifestyle modification or pharmacological treatment for metabolic risk factors.

The findings highlight the importance of incorporating thyroid function testing into the routine evaluation of individuals with MetS. Proactive screening and timely intervention may help reduce the risk of cardiovascular and metabolic complications in this high-risk group.

This study also brings attention to the need for further research. Future investigations should consider larger, multicentric populations and explore the impact of thyroid hormone replacement therapy on long-term metabolic and cardiovascular outcomes in patients with MetS. It is also vital to differentiate whether various thresholds of TSH or T4 levels within the subclinical range have differing effects on metabolic parameters, which may help in refining treatment guidelines. Early detection and timely management of thyroid dysfunction in patients with metabolic syndrome may play a crucial role in reducing the overall burden of cardiometabolic diseases within the population.

CONCLUSION:

Out of the 141 participants with metabolic syndrome, 122 individuals (86.5%) were found to have some form of hypothyroidism. Statistical analysis showed significant associations between hypothyroidism (both subclinical and overt) and several variables. Notably, significant relationships were observed with place of residence (p=0.01), hypertension (p=0.01), hypercholesterolemia (p=0.03), obesity (p=0.04), elevated LDL-cholesterol (p=0.05), raised C-reactive protein (p=0.04), uncontrolled diabetes mellitus (p=0.02), anemia (p=0.03), and hypomagnesemia (p=0.05). However, certain factors did not show a statistically significant association with hypothyroidism. These included age (p=0.48), gender (p=0.54), education level (p=0.08), smoking status (p=0.11), hyperuricemia (p=0.33),

and vitamin D deficiency (p=0.06).To conclude, findings add to the growing body of evidence that suggests a significant association between hypothyroidism especially in its subclinical form and metabolic syndrome. This relationship emphasizes the importance of a multidisciplinary approach in managing metabolic disorders, wherein endocrinologists, cardiologists, and primary care providers work in tandem to address the broader metabolic and hormonal profile of each patient. Early identification and appropriate management of thyroid dysfunction in MetS patients could represent a valuable step toward reducing the burden of cardiometabolic diseases in the population.

LIMITATION OF THE STUDY:

This study had some limitations that should be considered when interpreting the findings. It was conducted at a single healthcare facility and followed a cross-sectional design, which may limit how well the results apply to different or larger populations. The relatively small number of participants and the brief duration of the study also made it difficult to draw conclusions about long-term effects. To better understand the link between metabolic syndrome and hypothyroidism, future research should involve longer-term, prospective studies with diverse populations across multiple clinical centers. This approach would help strengthen the relevance and generalizability of the results.

AUTHOR'S CONTRIBUTION:

Collection and acquisition of data & grammatical corrections	*Dr. Syed Jahanghir*
Concept & design of study & proof read	*Prof. Dr. Muhammad Iqbal Shah*
Drafting the article and finalizing the manuscript	*Dr. Gulzar Fatima*
Revising critically and make it suitable for final format	*Dr. Maryam Iqbal*
Acquisition of data and grammatical review	*Dr. Pireh*
Drafting the article and finalizing the manuscript	*Dr. Ayesha Sajid*
Revision of the manuscript	*Dr. Moiz Muhammad Shaikh*
Analysis of data and drafting	*Dr. Syed Zulfiquar Ali Shah*
Final Approval of version	*By All Authors*

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