Original Article

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Internal Medicine Section

Thyroid Dysfunction and its Correlation with Metabolic Syndrome among Perimenopausal and Postmenopausal Women Attending a Tertiary Care Hospital in Karnataka: A Cross-sectional Study

MK VISHWAS[1], BN PHANESHWARA[2], UDAY RAGHAVENDRA[3], KV VASUDHA[4], B SHRUTHI[5]

ABSTRACT

Introduction: Thyroid dysfunctions are more common among women than men and increase near menopause. These are also associated with metabolic syndrome, increasing cardiovascular risk. These cardiovascular events and cerebrovascular events increase women's morbidity and mortality, especially after menopause. Though many researchers in the past few decades have tried to highlight this problem, majority of them have focused on the elderly population. Studies on women of the perimenopausal age group are still not frequently found.

Aim: To assess the correlation between thyroid dysfunction and metaoblic syndrome among perimenopausal and postmenopausal women.

Materials and Methods: A cross-sectional study was conducted among women attending the Medicine Outpatient Department (OPD) of Adichunchanagiri Institute of Medical Sciences, Nagara BG, Karnataka, India, from December 2017 to May 2019. Total 100 participants were included in the study, of which 50 were perimenopausal and 50 were postmenopausal women. Clinical history, examination and relevant investigations {Free T3 or Total T3, Free T4 or Total T4, Thyroid Stimulating Hormone (TSH)} were recorded. Association was studied using Chi-square test, groups were compared using Analysis of Variance (ANOVA) test, and correlation was estimated using Pearson's correlation test.

Results: Mean age of the study participants was 55.14±8.05 years. Thyroid dysfunction was observed in 17% of the participants, of whom 14% had subclinical hypothyroidism, 2% had overt hypothyroidism and 1% had hyperthyroidism. Prevalence of metabolic syndrome was 45%. There was a significant association of hypothyroidism with Fasting Blood Sugar (FBS) (p-value=0.005) and a positive correlation between FBS and TSH level and High Density Lipoprotein (HDL) with T3 and T4 levels.

Conclusion: Prevalence of hypothyroidism and metabolic syndrome were high among perimenopausal women and as FBS increases or HDL decreases, the chances of hypothyroid increases. Therefore, early identification and reduction of these components of metabolic syndrome decreases hypothyroidism and cardiovascular events.

Keywords: Cardiovascular risk, Fasting blood sugar, Hypothyroidism, Perimenopausal women, Thyroid function

INTRODUCTION

Among women, thyroid gland diseases are among the most prevalent disorders worldwide second only to diabetes [1]. Decreased thyroid function is more common among women particularly in postmenopausal women over 50 years, overt thyroid dysfunction is uncommon in women less than 40-year-old [2,3]. Thyroid Stimulating Hormone (TSH) levels do not vary with age in males but increases markedly in females after the age of 45 years [4]. The Whickman survey in the 1970s found 7.5% of adult women suffering from hypothyroidism and 2% suffering from hyperthyroidism (10 times more common than in men) [5]. Similarly, the Framingham heart study showed almost 12% of women over 60 years age had hypothyroidism [6].

Thyroid dysfunctions and metabolic syndrome are the two most common endocrine disorders with a substantial overlap in presentation, the risk of osteoporosis and Cardiovascular Diseases (CVDs) get magnified in postmenopausal women [7]. Thyroid disorders, if left untreated, will increase these risks [8].

Some clinical manifestations of menopause are similar to the signs and symptoms of thyroid dysfunction like hot flushes, sweating, heat intolerance, irritability, insomnia, palpitations, rapid changes in mood, increased bone fragility and fractures, and increased cardiac output and contractility, thus thyrotoxicosis can aggravate the underlying cardiac disease. It may mimic a state of hyperthyroidism [9,10]. While skin atrophy, brittle hair, constipation, periorbital oedema, and an increase in weight, with cognitive dysfunction, especially memory impairment, and occasional dementia may be observed in hypothyroid subjects [10]. Diagnosing and treating perimenopausal women with thyroid dysfunction include the difficulty of differentiating menopausal symptoms and symptoms related to thyroid dysfunction [11]. A study conducted in India in the year 2010 showed that 25-35% of the adult population is affected by metabolic syndrome, and the presence of metabolic syndrome is associated with thyroid dysfunction [12]. Though many researchers in the past few decades have tried to highlight the problem statement of metabolic syndrome the majority have focused either on the elderly population or the male population [12,13]. Studies on women of the perimenopausal age group are still not frequently found. There has been a dearth of literature on metabolic syndrome among women of this age group in this part of the country. Hence, the present study will look at the recent trends and highlight the importance of evaluation for metabolic syndrome among thyroid dysfunction patients and vice versa.

The primary objective of the present study was to assess thyroid function tests among perimenopausal and postmenopausal women attending a tertiary care centre in Karnataka. The secondary objectives were to assess factors related to thyroid dysfunction

among these women and to correlate thyroid function tests and components of metabolic syndrome among the study participants.

MATERIALS AND METHODS

A cross-sectional study was conducted in the General Medicine Outpatient Department (OPD), Adichunchanagiri Hospital and Research Centre, Balagangadharanatha Nagara, Mandya, Karnataka, India, from December 2017 to May 2019 as part of postgraduate research work. As the data collection was done by a single postgraduate trainee within a stipulated time with limited resources, it was predecided to include 100 perimenopausal and postmenopausal women attending the General Medicine OPD. Hence, purposive sampling was done. Ethical permission was obtained from Institutional Ethical Committee (AIMS/IEC/2017-2018). Informed consent was obtained from the participants before taking part in the study.

Inclusion criteria: All the perimenopausal and postmenopausal women attending OPD or getting admitted in General Medicine Department were included in the study.

Exclusion criteria: Patients who were critically ill, having chronic illness like Acquired Immune Deficiency Syndrome (AIDS), malignancy, tuberculosis, chronic kidney disease, Patient on medications like lithium, amiodarone, interferon-alpha, iodine and who refused to participate were excluded from the study.

Study Procedure

Study protocol included detailed clinical history, examination and investigations. Free T3 or total T3, free T4 or total T4, TSH and other tests were done to describe the various components of metabolic syndrome that included Fasting Blood Sugar (FBS), Serum triglycerides and serum High Density Lipoprotein (HDL). T3, T4 and TSH were measured by IMMULITE 1000 immunoassay. Fasting lipid profile was done with the ERBA XL300 autoanalyser. These tests were done in collaboration with the Department of Biochemistry of the Institute from the step of sample collection to reporting.

Operational definitions:

1. **Perimenopausal women:** Women having perimenopausal symptoms till one year of their last menstruation [14].
2. **Perimenopausal women:** Women who had their last menstruation atleast 12 months before the study period or if they had undergone surgical menopause [14].
3. The normal range for free T4 is 9-30 pmol/L (0.7-2.5 ng/dL), and for free T3 the range is 3.5-6.5 pmol/L (0.22-0.43 ng/dL). The normal range of the serum TSH was taken to be 0.4-4.2 mU/L. A person has thyroid dysfunction when the T3, T4 and TSH levels are above or below the normal range. Based on these values, patients were categorised as hypothyroid, hyperthyroid or euthyroid [15].

Metabolic syndrome was diagnosed when a patient had atleast three of the following five conditions according to the National Cholesterol Education Programme Adult Treatment Panel-III guidelines [16]:

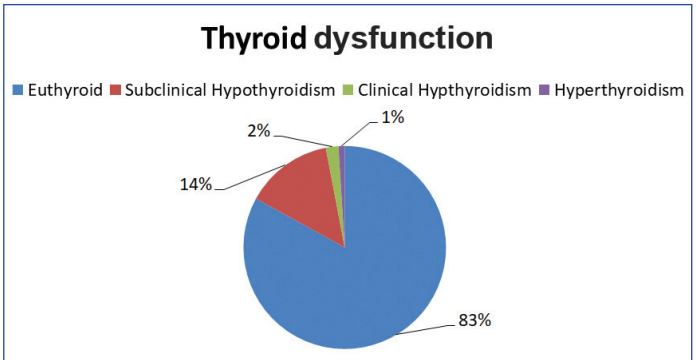
a. Fasting glucose ≥110 mg/dL (or receiving drug therapy for hyperglycaemia)
b. Blood pressure ≥130/85 mmHg (or receiving drug therapy for hypertension)
c. Waist circumference ≥80 cm
d. Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridaemia)
e. HDL-Cholesterol (HDL-C) <50 mg/dL (or receiving drug therapy for reduced HDL-C)

STATISTICAL ANALYSIS

Data was collected, entered in Microsoft excel sheet and analysed using Statistical Package for Social Sciences (IBM, Chicago) software version 20.0. Data was presented in frequencies, mean, standard deviation. Various groups (with three or more than three categories) were compared using Analysis of Variance (ANOVA). Correlation was established using Pearson's correlation test and association was studied using Chi-square test. A p-value <0.05 was considered to be statistically significant.

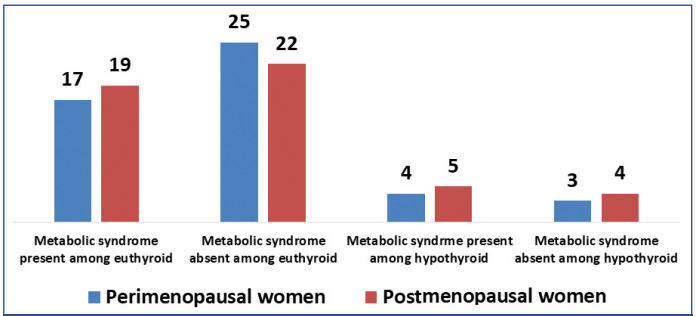
RESULTS

Among the 100 participants who participated in the study, 50 were perimenopausal and 50 were postmenopausal women each. Of total, 50% belonged to 45-54 years age group, 33% belonged to 55-64 years age group and 17% were more than 64 years. Mean age of the study participants was 55.14±8.05 years. Thyroid dysfunction was observed in 17% of the women, of whom 14% had subclinical hypothyroidism, 2% had overt hypothyroidism and only one had hyperthyroidism as shown in [Table/Fig-1]. Thyroid dysfunction was highest in 55-64 years age group where 8 (24.2%) out of 33 females were diagnosed with hypothyroidism. Most common clinical symptom in hypothyroidism was easy fatiguability (10 out of 16, 62.5%) followed by weight gain (8 out of 16, 50%). Most common sign was dry skin, alopecia, pallor (5 out of 16, 31.25% each). Overall, mean T3 was 1.28±0.66 pmol/L, mean T4 was 8.4±3.71 pmol/L and mean TSH was 3.77±2.87 mU/L. The mean TSH values were 8.74±4.34 mU/L among perimenopausal women and 9.31±3.34 mU/L among postmenopausal women. These values had no significant difference among perimenopausal and postmenopausal women (p-value >0.05).



[Table/Fig-1]: Prevalence of thyroid dysfunction among study population.

Prevalence of metabolic syndrome among study participants was 45% and it was higher among postmenopausal women (24 out of 50, 48%) compared to perimenopausal women (21 out of 50, 42%), however the difference was not statistically significant (Chi-square=1.004, df=1, p-value=0.316). Number of participants diagnosed with metabolic syndrome in each group has been shown in [Table/Fig-2]. Metabolic syndrome was higher among hypothyroid women (56.6%) compared to euthyroid women (43.4%), which was not statistically significant as shown in [Table/Fig-3]. The thyroid function with various patient characteristics has been shown in [Table/Fig-4].



[Table/Fig-2]: Prevalence of metabolic syndrome among thyroid dysfunction (hypothyroidism) in study population.

Thyroid dysfunction	Metabolic syndrome		Total (n)	p-value (Chi-square test)
	Absent n (%)	Present n (%)		
Euthyroid	47 (56.6%)	36 (43.4%)	83	0.476
Hypothyroid	7 (43.7%)	9 (56.3%)	16	
Hyperthyroid	1 (100%)	0	1	
Total	55 (100%)	45 (100%)	100	

[Table/Fig-3]: Distribution of metabolic syndrome and association with thyroid status among study participants.

DISCUSSION

Metabolic syndrome is a health issue of concern as various disorders has been linked with this. Thyroid functions are known to alter in various conditions but still remain unrecognised clinically in many of the cases and inconsistency in thyroid functions takes its toll with metabolic syndrome [12]. Overall, thyroid dysfunction was observed in 17% of the women, of whom 14% had subclinical hypothyroidism, 2% had overt hypothyroidism and only one had hyperthyroidism. Prevalence of metabolic syndrome was 45% and it was higher among postmenopausal women compared to perimenopausal women. No significant association was found between thyroid dysfunction and metabolic syndrome though prevalence was higher among hypothyroid women.

Variables	Perimenopausal (n=49)			Postmenopausal (n=50)		
	Euthyroid (n=42)	Hypothyroid (n=7)	p-value	Euthyroid (n=41)	Hypothyroid (n=9)	p-value
Age (years)	48.6±2.71	47.14±1.68	0.18	62.63±5.63	58.67±3.61	0.05
Pulse (bpm)	83.12±10.57	82.29±10.48	0.85	80.17±10.34	77.44±11.48	0.49
Systolic blood pressure (mmHg)	126.86±18.41	128.57±13.4	0.82	126.05±11.26	130.44±11.26	0.29
Diastolic blood pressure (mmHg)	81.71±11.65	82.29±7.34	0.90	81.17±8.22	85.33±5.1	0.15
Body mass index (kg/m^2)	26.77±3.67	28.13±3.56	0.37	25.98±3.81	28.83±2.7	0.04*
Random blood sugar (mg/dL)	158.26±42.53	193.71±50.14	0.05	182.85±88.79	208±98.02	0.45
Fasting blood sugar (mg/dL)	100.74±29.6	135.86±56.18	0.02*	121.66±64.06	138±57.46	0.48
Postprandial blood sugar (mg/dL)	157.95±52.57	218.43±98.11	0.02*	184.24±91.98	220.33±113.57	0.31
Total cholestrol (mg/dL)	184.73±37.39	194.71±58.98	0.55	185.49±45.22	230.22±73.68	0.02*
Triglycerides (mg/dL)	181.76±85.03	193.43±71.64	0.73	207.56±110.75	208.44±91.88	0.98
High density lipid (mg/dL)	51.99±15.4	54.57±12.31	0.68	51.59±10.15	51.56±9.88	0.99
Low density lipid (mg/dL)	94.94±39.76	111.43±48.01	0.33	108.48±44.25	125±26.04	0.29
T3 (ng/dL)	0.44±0.21	0.11±0.09	0.76	0.37±0.13	0.09±0.22	0.98
T4 (ng/dL)	2.71±1.12	0.23±2.65	1.22	2.54±2.37	0.45±0.97	0.11
Thyroid stimulating hormone (mU/L)	2.9±2.4	5.7±3.1	0.12	3.8±1.1	6.1±3.4	0.09

[Table/Fig-4]: Factors affecting thyroid status among study population.
*p-value <0.05 was considered statistically significant (Student's t-test)

In the present study, among 50 perimenopausal participants, 42 were euthyroid, seven were hypothyroid and one patient was hyperthyroid. Body Mass Index (BMI), Random Blood Sugar (RBS), FBS, Postprandial Blood Sugar (PPBS), total cholesterol, triglycerides, HDL, Blood Pressure (BP) were more in the hypothyroid women, with statistically significant difference in FBS, PPBS. Pulse was more in the euthyroid women but statistically not significant. Among the 50 postmenopausal women, 41 were euthyroid and nine were hypothyroid. Pulse was more in the euthyroid women compared to hypothyroid women but not statistically significant (p-value=0.49). BMI, TSH, Random blood sugar, FBS, PPBS, total cholesterol, triglycerides, low density lipoprotein and blood pressure were more in the hypothyroid women compared to euthyroid women of which the difference in total cholesterol and BMI were statistically significant [Table/Fig-4].

A significant association of hypothyroidism with FBS was observed [Table/Fig-5]. Positive correlation, though not very strong one, was observed in FBS and TSH. A low correlation of HDL with T3 and T4 levels were observed [Table/Fig-6].

Components of metabolic syndrome	Thyroid dysfunction		Total (n)	p-value
	Euthyroid (n=83) n (%)	Hypothyroid (n=16) n (%)		
Systolic BP (≥130 mmHg)	36 (43.4%)	11 (68.8%)	47	0.063
Diastolic BP (≥85 mmHg)	23 (27.7%)	7 (43.8%)	30	0.201
FBS (≥110 mg/dL)	22 (26.5%)	10 (62.5%)	32	0.005*
High density lipoprotein (<50 mg/dL)	38 (45.8%)	4 (25.0%)	42	0.124
Triglycerides (≥150 mg/dL)	40 (48.2%)	10 (62.5%)	50	0.295
Waist circumference (≥80 cm)	60 (72.3%)	15 (93.8%)	75	0.056

[Table/Fig-5]: Components of metabolic syndrome among different thyroid dysfunction groups.
BP: Blood pressure; FBS: Fasting blood sugar; HDL: High density lipoprotein
*p-value <0.05 was considered statistically significant (Chi-square test)

Components of metabolic syndrome	TSH		T3		T4	
	r-value	p-value	r-value	p-value	r-value	p-value
Systolic BP	0.038	0.710	-0.050	0.620	0.069	0.492
Diastolic BP	0.059	0.563	-0.074	0.462	0.017	0.867
FBS	0.275	0.006*	-0.111	0.271	-0.023	0.817
Triglycerides	0.068	0.504	0.013	0.899	0.139	0.167
HDL	-0.153	0.128	0.284	0.004*	0.336	0.001*
Waist circumference	0.095	0.352	0.113	0.264	-0.053	0.604

[Table/Fig-6]: Correlation between thyroid profile and components of metabolic syndrome.
TSH: Thyroid stimulating hormone; BP: Blood pressure; FBS: Fasting blood sugar; HDL: High density lipoprotein
*p-value <0.05 was considered statistically significant (Pearson's correlation)

Mean age of the study participants was 55.14±8.05 years which was similar to Butmarasri K et al., study (56±4.7 years) [17]. The present study showed 17% prevalence of thyroid dysfunction of which 14% were subclinical, 2% overt hypothyroidism and 1% hyperthyroidism. While the study done by Butmarasri K et al., hypothyroid women were 12.9%, and hyperthyroidism was 3.2% which was slightly higher than the present study [17]. Many studies showed higher prevalence of hypothyroidism than hyperthyroidism. Study done by Latha P et al., among perimenopausal women, showed hypothyroidism was 18%, overt hypothyroidism was 1% and subclinical hypothyroidism was 17% [18]. In the study done by Joshi SA et al., among pre and postmenopausal women, hypothyroidism was found to be 12.5%, in that overt hypothyroidism was 1.5%, subclinical hypothyroidism was 11% [19]. Overall, it has shown that thyroid dysfunction increases near menopause and

more so after the menopause [20]. Mean TSH value was 8.74±4.34 mU/L among perimenopausal women in the present study which is similar to Garg N et al., where they had observed a mean TSH of 8.24±1.3 mU/L but much higher as compared to results of Latha P et al., [21,18]. Mean TSH among postmenopausal women was 9.31±3.34 mU/L which was again comparable to Garg N et al., but much higher than study done by Kamal SV et al., [21,2].

Prevalence of metabolic syndrome was 45% in the present study and it was higher among postmenopausal women (52%) compared to perimenopausal women (42%). A study done in China among adult women showed 23.2% prevalence of metabolic syndrome while a study in Iran [22] showed the prevalence of metabolic syndrome of 44.9% among premenopausal women and significantly increased to 57.9% and 64.3% in early menopausal and postmenopausal women respectively which is in line with the present study, while Indhavivadhana S et al., study shows much lower prevalence (12.4%) among premenopausal women [23]. Metabolic syndrome among euthyroid postmenopausal women was 52.48% which was much lower compared to Heidari R et al., (64.3%) and Jeyasheela K et al., (64%) studies whereas higher than Sieminska L et al., (47%) [22,24,25]. Metabolic syndrome among hypothyroid postmenopausal women was similar to Sieminska L et al., (49%) and Kannan L et al., (51.8%) [25,26].

Younger age, high BMI and higher total cholesterol were significantly associated with hypothyroidism only among postmenopausal women, while higher FBS and PPBS were significantly associated with hypothyroidism among perimenopausal women in the present study. Among the components of metabolic syndrome, FBS had positive correlation with TSH and negative with T3, T4 and HDL had negative correlation with TSH and positive correlation with T3, T4. Hypothyroidism has higher chances of developing metabolic syndrome though it was not statistically significant in the present study which was similar to China study [20]. Study by Chakradhar M et al., showed that metabolic syndrome was significantly associated with thyroid dysfunction (p-value=0.032) [13]. Deshmukh V et al., observed that the predominance of hypothyroidism suggests Metabolic syndrome could be a consequence of various grades of hypothyroidism during the natural course of disease [27].

Chakradhar M et al., study also showed that higher FBS and increased waist circumference were found to be statistically significant with thyroid dysfunction (p 0.033 and 0.039 respectively) and waist circumference showed a positive correlation with TSH and a negative correlation with T4 [13]. Gyawali P et al., depicted a significant association between waist circumference and T4 (p-value=0.002) but not with TSH (p-value=0.136) [28]. This difference may be due to the genetic, environmental factors and intake of iodine, which is likely to vary between different geographical areas.

Increased prevalence of hypothyroidism among patients with metabolic syndrome may have an ill effect on the cardiovascular health by increasing lipid levels and hypertension. Increased risk of cardiovascular events and cerebrovascular events may be seen in patients with metabolic syndrome and dysfunction of thyroid gland [13]. Therefore, early identification of thyroid dysfunction among women with diabetes and increased waist circumference and impaired lipid profile may help in reducing cardiovascular events in the long run.

Association with thyroid dysfunction with different components shows significant association with FBS (p-value=0.005), and as waist circumference increases, chances of hypothyroidism also increased in Khatiwada S et al., study [29]. As systolic and diastolic blood pressure and triglycerides increase and as HDL decreases hypothyroidism increases, though it was not statistically significant. TSH value shows positive correlation with FBS and T3, T4 show positive correlation with HDL and TSH shows negative correlation similar to Khatiwada S et al., study [29]. This may be due to the associated insulin resistance and impaired glucose tolerance in those patients [30].

Similarly, Abd El-Hay GE et al., showed that triglyceride level in the blood had significant positive correlation with TSH (p-value=0.02), and FBS had significant positive correlation with T3 (p-value=0.02), also triglyceride level in the blood has significant positive correlation with T4 (p-value=0.02), and waist circumference has significant negative correlation with T4 [31]. Delitala AP et al., also stated a positive correlation between TSH with triglycerides, free thyroxine with HDL, and blood pressure with FBS while FT4 had negative correlation with waist circumference [32].

Thyroid dysfunction was associated with high waist circumference (99.17%), reduced HDL (87.60%), raised Homeostasis Model Assessment-Estimated Insulin Resistance (HOMA-IR) (86.78%), higher systolic blood pressure (77.69%), higher diastolic blood pressure (59.50%), raised FBS (58.68%), and raised triglycerides (33.06%) in Deshmukh V et al., study [27]. BMI, waist circumference, triglycerides, blood pressure in the subclinical and overt hypothyroidism groups were significantly higher in a study done by He J et al., [20].

Study in postmenopausal women in Poland showed on comparing subclinical hypothyroid women with and without metabolic syndrome, subjects with metabolic syndrome had higher BMI, abdominal circumferences, waist hip ratio and HOMA-IR. They presented with higher blood pressure. Serum concentrations of cholesterol, triglycerides, fasting glucose, Interleukin-6 (IL-6), TSH, Thyroid-Antibodies were also higher and serum HDL was lower [25].

Effect of thyroid hormones on the metabolism of lipid could be explained through induced transcription of low density lipoprotein receptor gene, expression of hydroxyl methylglutaryl coenzyme A reductase, and finally upregulation of sterol regulatory element binding protein-2, also reduction in level of FT4 is associated with visceral obesity and increased insulin resistance [32]. It is a known fact that TSH is involved in the lipid metabolism and promotes accumulation of fat in the intra-abdominal region, which will be expressed as increasing waist hip ratio and waist circumference. In subjects with higher TSH, different processes in adipose tissue such as adipogenesis, lipogenesis, and lipolysis could be perturbed [33]. Thyrotropin stimulates adipogenesis by activation of preadipocyte differentiation, and increases adipocyte hypertrophy by triglycerides synthesis in mature adipocytes via TSH receptor expression in adipose tissue [33]. This explains higher waist circumference in hypothyroid women. However, studies also exists which report no association between thyroid profile and metabolic parameters [34-36].

Limitation(s)

One of the limitations of the study was that the sample size was not calculated. The study was done by a single postgraduate trainee within a stipulated time with limited resources. The researcher wish to continue the study at community level to minimise the selection bias as only patients visiting the health facility have been included here. Comparison of the result with the age-matched male population will help to highlight the gender difference in the natural history of metabolic syndrome and thyroid dysfunction.

CONCLUSION(S)

In the present study, it was evident that the metabolic syndrome was more found in women with hypothyroidism. Hence, importance of early detection of thyroid dysfunction, particularly to diagnose the disease in the subclinical stage itself could not be denied. Larger population follow-up studies are needed to generate evidence to support screening to facilitate early interventions among women. The authors wish to continue the study with larger population to overcome the shortcomings of the current study.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of General Medicine, Adichunchanagiri Medical College, Mandya, Karnataka, India.
2. Assistant Professor, Department of General Medicine, Adichunchanagiri Medical College, Mandya, Karnataka, India.
3. Postgraduate Student, Department of General Medicine, Adichunchanagiri Medical College, Mandya, Karnataka, India.
4. Postgraduate Student, Department of General Medicine, Adichunchanagiri Medical College, Mandya, Karnataka, India.
5. Associate Professor, Department of General Medicine, Adichunchanagiri Medical College, Mandya, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. MK Vishwas,
Assistant Professor, Department of General Medicine, Adichunchanagiri Medical College, BG Nagar, Mandya, Karnataka, India.
E-mail: drvishwasgowda@gmail.com

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