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RESEARCH ARTICLE

STUDY OF THYROID DYSFUNCTION IN METABOLIC SYNDROME IN TAMILNADU

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ABSTRACT

Metabolic syndrome predisposes the Non Communicable diseases especially cardiovascular disease. The thyroid dysfunctions also induce lipid profile abnormality and enhance the atherosclerotic disease. Thyroid dysfunction is not included in the diagnostic criteria for metabolic syndrome. However when it occurs concomitantly significantly increases cardiovascular risks.

In this study, in the selected patients with metabolic syndrome, the presence of associated thyroid dysfunction among them and the frequency of prevalence of the components were studied and correlated. First 100 patients both men and women attending for NCD checkup in our Government Kanyakumari Medical College Hospitals with Metabolic syndrome as per modified (NCEP – ATP III criteria) in the last one year is included in the study. As a cross section control study equal number of matched patient without metabolic syndrome attending the casualty are included as control. After obtaining approval of Ethics Committee of the institution, for all these patients Fasting blood sugar, Lipid profile, and Thyroid function test were (TSH and FT₃) carried out along with measurement of Body mass index (BM), blood pressure and waist circumference.

In the 100 metabolic syndrome patient included in this study overall 42% had subclinical hypothyroidism and 26% overt hypothyroidism rest 32% were Euthyroid. However in women 55% of them had subclinical hypothyroidism and 23% overt thyroid, 22% were Euthyroid.

Central obesity is high in post menopausal women and also HDL cholesterol.

Our study concludes, majority of patients with metabolic syndrome have thyroid dysfunction and more so females have more thyroid dysfunction. Patients with obesity and diabetes mellitus had more evidence of Hypothyroidism. Metabolic syndrome with thyroid dysfunction precipitates the atherosclerotic heart diseases. It is recommended to include thyroid function estimate as a mandatory study in people with metabolic syndrome.

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INTRODUCTION

The clusters of hypertension, hyperglycemia, gout and android obesity were noted and reported in 1920 by Kylin E (1) and in 1947 by Jean Vague (2). The term Syndrome “X” was used by Hermans Haller, in 1977. In 1988, during the seminal Banting lecture, Reaven described this as Insulin resistance syndrome. (3)

Person with constellation of high blood pressure, abdominal obesity, impaired lipid profile, impaired fasting glucose level as a cluster are termed as having Metabolic Syndrome(3) in 1999 by WHO(4). Various diagnostic criteria's are postulated by WHO, NECP (ATP III) and American Association of clinical Endocrinology definition etc. (5).

Thyroid dysfunction is defined as the altered thyroid stimulating hormone level with normal or altered thyroid hormone.

Raising life expectancy resulting in increasing population of old age, innovative physical automations leading to physical inactivity, improper food and junk eating increasing the incident of obesity and the raising insulin resistance all contribute for the alarm raise in the metabolic syndrome.(6)

People having metabolic syndrome are having double risk of developing cerebrovascular disease and four times risk of developing type II diabetes. In various studies in India 25 to 35% adults are affected by metabolic syndrome. (7)& (8)

The Prevalence of Cardiovascular disease is 2-3 times higher in individuals with metabolic syndrome than in age matched controls. (9) The earlier identification of predictive factors of syndrome like hypertension and obesity can prevent diabetic and cardio vascular disease

Several studies have proved existence of an association with metabolic syndrome and thyroid stimulating hormone level.

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People with high TSH level have more than two fold increase in the development of metabolic syndrome. (10)

It is also observed and studied, subclinical hypothyroidism with increased TSH level is associated with increased risk of coronary Heart Diseases. Hypothyroidism has been associated with atherosclerosis and hyper cholesterolemia. (11)

As noted TSH dysfunctions and metabolic syndrome are being independent risk factors in the development of atherosclerotic Cardio Vascular Disease (CVD), the existence of both in an individual concurrently will increase the incidence of cardiovascular risk in the individual. (12)

Gamberg *et al* reports an excessive deficiency of thyroid hormone can cause cardiovascular disease and aggravate many preexisting conditions. (13)

Nah EL *et al* have shown than total cholesterol and atherosclerotic tendency is high in females with hypothyroidism. (14)

PrabinGyawali has provide that coexistence of thyroid dysfunction and metabolic syndrome might substantially increase the atherosclerotic cardiovascular disease. Thyroid dysfunction is a risk factor for atherosclerotic cardio vascular disease mediated by the effects of thyroid hormones on lipid metabolism and blood pressure (15). Component of metabolic syndrome also leads to atherosclerotic cardiovascular disease.

In his study Kok-Yong Chin *et al* proved that thyroid stimulated hormone exerts independent effect on lipid metabolism by inducing adipogenesis, lipolysis and increasing the activity of HMG CoA. Thyroid hormones exert effect on Total cholesterol, LDL-C and HDL-C while thyroid stimulating hormones on Triglycerides (16).

The present study was carried out to understand and determine the presence of thyroid dysfunction on diagnosed patients with Metabolic syndrome in our Government Medical College with positive objective of early correction of thyroid dysfunction can have impact on the complications of Metabolic syndrome

MATERIALS AND METHODS

The study was conducted from January 2014 to December 2014. First 100 patients with Metabolic syndrome attending the NCD clinic in Government teaching hospital were included for the study with 100 patients attending causality OPD with same age and sex distribution are taken as control on selective random basis.

Inclusion criteria

Patient with metabolic syndrome are diagnosed based on the criteria by the American National Cholesterol Education Programme Adult III treatment and (NCEP- ATP III- 2001) and the modified ATP III guideline on central obesity.(17) The participants having at least three components of an NCEP ATP III definition of Metabolic Syndrome are included in the study

1. A fasting of blood glucose level above 100mg/dl (56mmol/L)
2. A fasting triglyceride level of 150mg/dl or greater
3. An HDL-C level lesser than 40mg/dl in men (1mmol/L) and less than 50mg/dl (1.3mmol/L) in women
4. Blood pressure of 130/85mm of Hg or above
5. Waist circumference in men >90cm and in women > 80cm

Exclusion Criteria

1. Pregnancy
2. Significant comorbid Renal and Hepatics disease or Myocardial Infarction
3. Patient on chronic drug usage (Steroid/anti-psychotic/ anti-depressant/ OCP)
4. Immobile patients
5. Patients showing non willingness for the study
6. Patient taking medication for lipid orthyroid disease

Ethical Aspects

The study proposal was approved by the Ethical Committee of our institution. All participants were provided and obtained written informed consent after explaining all the features of study.

The patient attending NCD OP with inclusion criteria are enrolled and all the values are reassessed using single window approach. Their baseline demographic data were collected and detailed physical examination was done. Blood pressure was measured in the right arm in the supine position. The waist circumference was measured at the narrowest indentation between the costal margin at 10th rib level and anterior superior iliac spines while the patient is standing with bare skin and at mid expiration. Weight and height were measured with light cloths and no shoes and Body mass index calculated.

Biochemical values of TSH, Free T4, Fasting plasma glucose, 2 hours Post prandial glucose, Triglyceride , Total cholesterol, LDL – C, HDL-C were measured using standard procedures and values were documented.

Definitions

i)	Sub clinical Hypothyroidism:	High serum TSH with normal Free T4
ii)	Overt Hypothyroidism	TSH levels are high(TSH > 10µIu/ml) and low FT4 (FT4 <0.93ng/dl)
III)	Euthyroid	Normal TSH levels (0.4 to 4.5 µIU/ml) and normal FT4 (0.93-1.7ng/dl)

IV) Metabolic Syndrome As per NECP ATP – III Guideline.

RESULTS

The study was conducted for 100 patients with Metabolic syndrome and 100 in control group.

Mean age for the study population was **53.6 ± 10.20** and for the control group **52.6 ± 10.50**.The age distribution is shown in Tab. (1) /Fig. (1). Total number of female in study population

were 61 and in control group 58 and Male in study population were 39 and in control group 42.

Tab. 1 Age/Sex Distribution of patients included in study and control group

Age in Year	study group			control group		
	Male	Female	Total	Male	Female	Total
20-30	0	2	2	2	2	4
30-40	3	5	8	6	6	12
40-50	13	20	33	10	20	30
50-60	17	20	37	18	20	38
60-70	6	14	20	6	10	16
Total	39	61	100	42	58	100

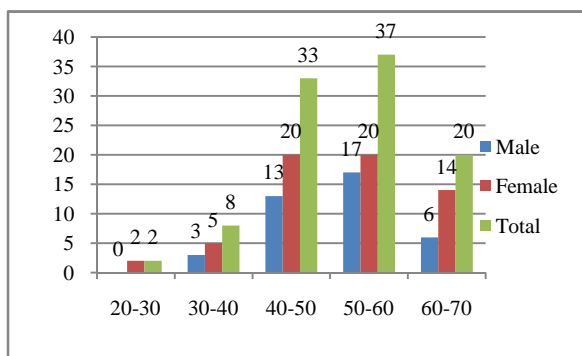


Fig. I (a) Age/Sex Distribution of patients included in study group

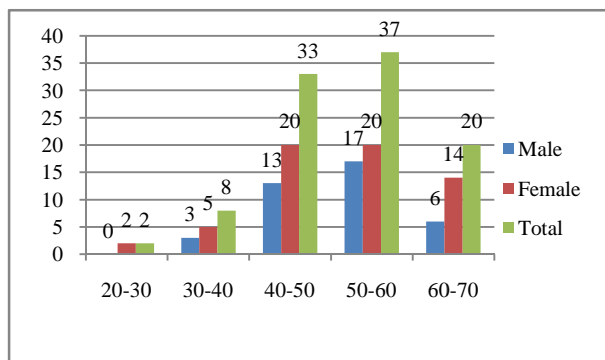


Fig. I (b) Age/Sex Distribution of patients included in control group

Tab. 2 Presence of Metabolic Components in Male/Female with Mean and SD.

Components of Metabolic syndrome	Male		Female		Total 100%	Mean & SD
	No.	%	No.	%		
1) Fasting Blood Sugar >100mg/dl	23	59	38	62	61	156 ± 26.7
2) Triglyceride >150mg/dl	25	64	38	61	63	178 ± 36.4
3) HDL < 40mg M <50 in F)	10	26	50	82	60	48.7 ± 18.08 56.4 ± 21.07
4) Waist circumference > 90cm in Male and >80cm in Female	28	71	55	90	83	102.6 ± 4.2 96.3 ± 3.6
5) Blood pressure >130/85 mm of Hg	30	76	45	74	75	136.6 ± 16.57 89.3 ± 13.02

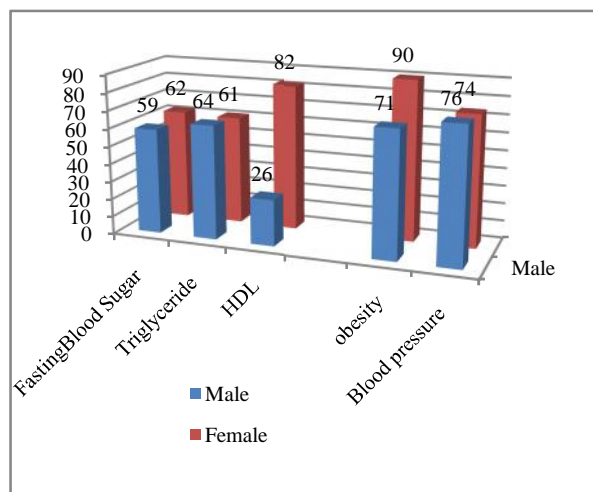


Fig. 2 Presence of Metabolic Components in Male/Female Thyroid Function Test

Tab 3 Mean and SD values of TSH & FT4 in both study and control group

	Study Given Mean ± SD	Control Given Mean ± SD
TSH (µIU/ml)	11.92 ± 21	4.3 ± 6.3
TF4 (ng/dl)	1.16 ± 0.32	1.4 ± 0.56

Based on the definition for subclinical and overt hypothyroidism the patients are grouped together as having subclinical hypothyroid, overt hypothyroid and Euthyroid and tabulated both from study and control group. (Fig. 4a & b, Tab. 4)

Tab. 4 Number of patients included in three categories

Thyroid Status	Study Group			Control group		
	Male	Female	Total	Male	Female	Total
Thyroid Status	39	61	100	42	58	100
Sub clinical Hypothyroid	12	40	52	1	10	11
Overt Hypothyroid	7	15	22	1	9	10
Euthyroid	20	6	26	37	42	79

Individual Components of Metabolic Syndrome in the study subjects

The Individual components of Metabolic Syndrome were studied separately for the patients and are tabulated in Tab. 2 & Fig. 2

For all the patient in study group and control group Thyroid stimulating hormone level and free T4 measured using standard method The results of thyroid function test in both group were analyzed the mean value and standard deviations are calculated as in tabulated in Tab. 3

Association of components of metabolic syndrome with thyroid dysfunction

Having grouped the participants, presence of each components of metabolic syndrome in patient with subclinical, overt and euthyroid conditions were studied separately in both male and female and tabulated. Tab 5&6

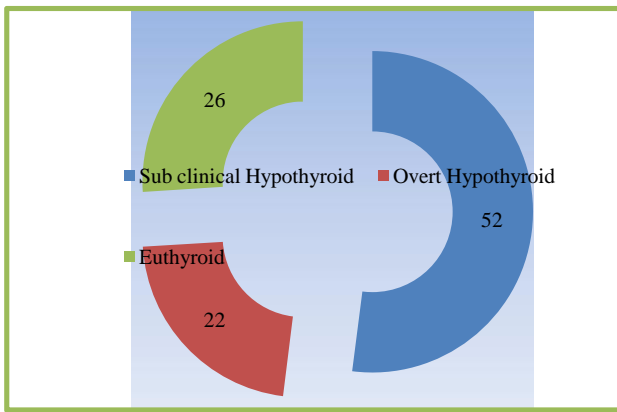


Fig.4 a Thyroid dysfunction in study group

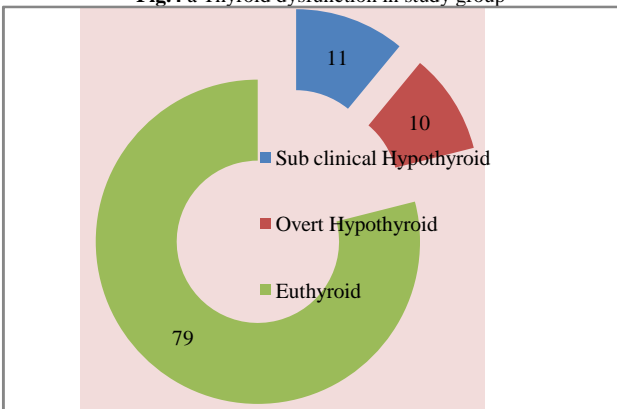


Fig. 4 b Thyroid dysfunction in control group

DISCUSSIONS

Metabolic syndrome constitute a cluster of risk factors characterized by hypoglycemia, atherogenic dyslipidemia, symptomatic hypertension, prothrombotic and proinflammatory conditions. (16)

As per our study metabolic syndrome is characteristically more common in female (61%) than male (39%). This is in consistent with other reported studies.

Metabolic syndrome incidence increases with age and our mean age was **53.6±10.20**. From our study we found peak incidence is in 50-60 age groups. *Otamen et al* in his study also published the peak incidence of age in male 52-84 ±12.47 and female 52.78 ± 12.33. (20)

However with risky life style behavior with less activities, inadequate exercise and excess intake of junk food even in younger age group of 20 – 30, we do get patient with metabolic syndrome. There is no significant difference in the age group of metabolic syndrome in male and female our study shows component predisposition of Metabolic syndrome varies from female to male. The most common component which affect both male and female is **central obesity**. Though the NCEP III guideline state criteria for waist line measurement as more than 102 cm for male and >88 for female as obesity, the amended criteria for South Asians especially South India populations are >90 cm for male and >80 cm for female.

Tab 5 Number of patients with each component in Female

S.No.	Components of Metabolic syndrome in Female patients in study group	Sub clinical Hypothyroidism (40)	Overt Hypothyroidism (15)	Euthyroid (6)	Total (61)
1	FBG > 100MG/DL	31	12	5	48
2	Triglyceride >150mg/dl	30	14	4	48
3	HDL-C <50 mg /dl Female	36	15	5	56
4	Waist circumference area >80cm Female	36	14	5	55
5	BP > 130/85mmof Hg	33	12	5	50

Tab. 6 Number of patients with each component in male

No.	Components of Metabolic syndrome Female patients in study group	Sub clinical Hypothyroidism (12)	Overt Hypothyroidism (7)	Euthyroidism (20)	Total (39)
1	FBG > 100mg/dl	10	3	7	20
2	Triglycerides >150mg/dl	11	4	8	23
3	HDL-C >40 mg/dl	3	1	1	5
4	Waist area >90 cm	10	6	12	28
5	BP > 130/85mmof Hg	10	5	11	26

In our study we have followed this modified NCEP III guidelines. (21)

Obesity constitutes the major risk factor for female than male. In male the percentage of obesity is 76% while in female it is more than 90%. The low HDL level is also predominantly seen in female 82% while in male with metabolic syndrome only 26% is having low HDL. In his study *GhanaFareedKow et al* in pre and post menopausal women has proved that post menopausal women had significant increase in the waist circumference. (22). In our study also Increased waist circumference in female are more seen in post menopausal women than in premenopausal

On analyzing the thyroid profile in all the patients in the study group thyroid dysfunction is significantly higher in female than

	Male %	Female %
D.S. Prasad , Z. Kabir <i>et al</i> 2012 in Orissa(39)	34.2	65.8
Ayesha A. Motalaetal South Africa 2009(40)	39	62
Jayakumar R.V. <i>et el</i> (37) North India	34	66
UnaidilaBG <i>et al</i> Nigeria 2009 (19)	32	68.9
Present study – Dr. J..A. Jayalal <i>et al</i> 2014	39	61

	No. of patient	Obesity	HDL	Triglycerides	Blood sugar	Hypertension
Jayakumar <i>et al</i> Delhi(.37)	120	120	75	67	47	69
Gaurav <i>et al</i> , Chennai(24)	79	76	57	56	59	50
Present study J.A. Jayalal <i>et al</i> 2014	100	90	82	61	62	74

male group. Subclinical hypothyroidism present in 65% (40 patients) of total 69 female with metabolic syndrome and also overt hypothyroidism present in 24.5% (15 patients). Only 6 patients (10%) were euthyroid. However the presence of thyroid dysfunction is much less in male. Sub clinical hypothyroidism present in 30% (12 patients) out of 39 male patient with metabolic syndrome, overt hypothyroidism in 17% (7 patients) and the rest 56% (22 patients) are euthyroid..

Irwin Klein *et al* in their study on Cardiovascular effects of hypothyroidism update March 2015 stated hypothyroidism directly alters cardiac function through changes in myocyte specific gene expression. They also make significant changes in the atherosclerotic risk factors including hyper cholesterolemia, diastolic dysfunction, carotid intimal media thickness and endothelial derived relaxation factor (nitric Oxide) which accompany overt hypothyroidism. (23)

Gaurav Agarwal, Sudhakar M.K *et al* in their study conducted in tertiary care teaching hospital in Chennai on 76 female patients with metabolic syndrome, concluded females with metabolic syndrome have a high prevalence of thyroid dysfunction which predisposes them to cardiovascular events. (24).

Jayakumar RC *et al* in their study conducted in an endocrinology clinic with 120 patients, 52 had subclinical hypothyroidism, 12 had overt hypothyroidism, 6 had goiter and 2 had multi nodular. Goiter and 48 patients were euthyroid (25).

In over study out of 100 patients 52 had subclinical hypothyroidism, 20 have overt thyroid and 25 were euthyroid.

Chubb *et al* showed that the estimated cardiovascular risk at 10 years for patient with insulin resistant at a TSH level 1mIU/ L was almost half of that of TSH 5mIU/L (26).

In our study in the control group having 100 patients attending casualty subclinical hypothyroidism is seen in 11 patient and overt hypothyroidism in 10 patient and 79 patient were euthyroid. A recent study by **Villar *et al*** has identified the prevalence of sub clinical hypothyroidism to be 4% to 8% in male general population and 15% to 18% in women. (27)

In Rotterdam study it is revealed women with subclinical hypothyroidism and normal lipids had higher Ischaemic Heart Disease and aortic atherosclerosis. (28)

Sat Byul in his study in Korea state there is relationship between thyroid function and cardiovascular risk factors and higher levels of TSH may predict metabolic syndrome. (29)

SakirOzgunKezkek in his study in Turkey also says frequency of thyroid dysfunction is higher in metabolic syndrome. (30)

Higher TSH levels and sub clinical hypothyroidism > 100mIU/L increases odds of prevalent but not incidence of metabolic syndrome says **Waring A.C *et al*** AC in his study. (31)

Shantha *et al* also in their study from South India has shown overt and sub clinical hypothyroidism has increased risks in female with metabolic syndrome. Patient will have increased C. reactive proteins which is the sign of systemic inflammation. (32)

Chugh *et al* however differs and state elevated TSH in metabolic syndrome is a consequent of metabolic syndrome rather than a state of subclinical hypothyroidism. (33)

In our study among the components of the metabolic syndrome, patients having increased waist circumference (obesity) has more positivity for subclinical Hypothyroidism. Incidences of thyroid dysfunction in diabetic patient are also more.

Reaven *et al* way back in 1988 states, Role of insulin resistance in human disease and incidence of thyroid disease are significantly higher in diabetics. (3)

There is a direct link between thyroid profile and insulin sensitivity. Insulin resistance is the key pathologic factor for the progression of metabolic syndrome. Insulin resistance is the cardinal promotive factor for Type 2 diabetes mellitus, dyslipidemia and thyroid dysfunction. **Singh BM *et al*** in their study conducted in females in a tertiary care hospital in Delhi concluded that there is significant correlation between TSH and insulin (34)

Insulin resistance may lead to state of increased hepatic cholesterol production and very low clearance of low density lipoprotein and increased clearance of HDL. **Bakker. S.J.L *et al*** in their study conducted in Healthy individual stated insulin resistance increases the deleterious effect of hypo thyroidism on lipid profile. (35)

Overt Hypothyroidism and subclinical hypothyroidism are established risk factors for hyperlipidemia insulin resistance, hyper coagulability and low grade inflammation. (36)

The complex interplay between insulin resistance and thyroid dysfunction results in diabetic dyslipidemia .The link between thyroid hypo function and dyslipidemia are well established in several studies. More than 90% with overt hypothyroidism will have hyper lipidiemia. Thyroid hormones regulate the metabolism and mobilization of lipids in the body. Hypothyroidism results in increased total cholesterol, apolipo protein, triglyceinde and low density lipo protein. Cell surface LDL receptors are responsible for LDL clearance from serum. In hypothyroidism this cell surface LDL receptors are reduced and there by decrease the biliary excretion of cholesterol, this result in elevation by serum LDL and VLDL levels. As it also has the effect to decrease the lipo protein lipase activity cause triglyceridemia. (37)

Bakker.S.J.L and Maaten.J.C.in their studies conducted in 47 healthy individuals with Euthyroid status stated that the concentration of Free triiodothyronine (FT3) were associated with insulin production and Hyperinsulinemia and it is a new determinant of blood pressure in healthy individuals (35)

Cardiovascular manifestation is frequent in thyroid dysfunction. Both hyper thyroidism and hypothyroidism plays a role in various cardio vascular manifestations like increased heart rate, flutter, fibrillation to atherosclerosis.

Subclinical thyroidism induces enhanced risk for atherosclerosis and myocardial impacts. Treatment with therapeutic dose of thyroxin for this patient not only improves the hypothyroidism but also significantly cardio vascular risks.

Several studies have stated metabolic syndrome and thyroid dysfunctions both enhances the atherosclerotic cardio vascular disease. Our study shows majority of female patients with metabolic syndrome also have subclinical (or) overt hypothyroids, hence at a high risk of atherosclerotic cardio vascular disasters. However as studies prove early identification and therapeutic interventions for thyroid dysfunction can halt the progressions of enhanced cardiovascular risks in patients with metabolic syndrome.

As for the existing criteria's for metabolic syndrome, testing for thyroid functions is not included as criteria. But majority of these patients have thyroid dysfunction especially in female patients comparing to the control group of same sex and age group.

CONCLUSION

The study concludes that female with metabolic syndrome have higher incidence of thyroid dysfunctions, together which can lead to early progression of deleterious cardiovascular events. Hence we recommended the thyroid dysfunction shall be included as a criterion for the diagnosis of metabolic syndrome or else the entire patient with metabolic syndrome shall be subjected to thyroid profile study.

Competing Interest

The authors declare that they have no competing interest.

Future Recommendation

Large study to determine the effect of thyroid dysfunction on metabolic syndrome and role of early replacement of thyroid deficiencies in metabolic syndrome shall be under taken to make positive impact in the raising NCD

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