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Latest Insight into the Relation of Metabolic Syndrome with Thyroid Dysfunction

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Abstract

The Metabolic syndrome is a modern epidemic and is considrred to be one of the major public health issues of this century. It is constellation of physical conditions and metabolic abnormalities commonly found in association with increased risk for development of Type II diabetes mellitus, cardiovascular disease and other medical conditions. Thyroid hormones play an important role in regulating energy homeostasis. In addition, thyroid hormones can regulate lipoprotein, glucose metabolism and blood pressure. Thus there is possibility of thyroid dysfunction (may be cause or effect) having an association with metabolic syndrome and its component. The study was aimed to find out occurrence of metabolic syndrome in hypothyroid patients and to determine the association between the components of metabolic syndrome and thyroid hypofunction.

Index terms— thyroid, hyperthyroidism, hypothyroidism, subclinical, lipoprotein. TRH (thyroid releasing hormone), TSH (thyroid stimulating hormone).

Patients receiving any medication that may alter thyroid function and lipid profiles.

Thyroid Hormones are important for multiple reasons. Thyroid hormones play an important role in regulating energy homeostasis. 1 They can stimulate expression of uncoupling proteins in the mitochondria of fat and skeletal muscle, modulate adrenergic receptor numbers by enhancing responsiveness of catecholamine, and thus regulate metabolic rate and body weight. 2 In addition, thyroid hormones can regulate lipoprotein and glucose metabolism and blood pressure. Thyroid function testing is obtained more frequently than any other endocrine screen in the evaluation of thyroid dysfunctions. The synthesis of thyroid hormone is almost entirely T 4 , but as iodine becomes scarce, the synthesis of T 3 increases.T 3 is the more active form of the hormone, and peripheral tissues can regulate the conversion of T 4 into either T 3 (more active) or rT 3 (not active). Thyroid hormones increase the metabolic rate of most tissues. Although it does not affect the metabolic rate of nervous tissue, it is absolutely necessary for postnatal brain maturation. TSH is regulated mainly by circulating T 4 , but the T 4 entering the thyrotrophs must be converted to T 3 before it affects the negative feedback loop. Thyroxine causes: Hyperthyroidism results from the excess synthesis of thyroid hormones by the thyroid gland. The prevalence of hyperthyroidism in the general population is about 0.5% and is associated with the Graves disease in 80% of cases. Other causes include toxic modular goitre, thyroid and pituitary adenomas, thyrioditis, use of exogenous thyroid hormones, thyroid carcinoma, hydatiform moles and stromal ovaries. Signs and symptoms of hyperthyroidism includes increases appetite, weight loss, palpitation, tachycardia, frequent bowel movements, menstrual disturbance, muscle weakness and catabolism of muscle protein, exophthalmia, lid lag, infrequent blinking and hyperactive deep tendon reflexes. In case of thyrioditis, patients may experience pain and tenderness in the thyroid region. ? Increase in BMR ? Increase in(D D D D) F b) Hypothyroidism

Hypothyroidism results from the inadequate production of thyroid hormone, and is classified as clinical or sub-clinical depending on the degree of clinical severity and the extent of abnormalities in thyroid indices. In overt or clinical hypothyroidism hormones level are low and TSH is elevated. Subclinical hypothyroidism describes a condition in which T 3 and T 4 levels are normal but TSH is elevated, or the TSH response to

TRH infusion is exaggerated. The prevalence of clinical hypothyroidism is approximately 2% in women and less than 0.1% in men. 5 The significantly higher rate of hypothyroidism in women may reflect the stimulating effect of female reproductive hormones on immunologic function, producing greater rate of autoimmune disease in women. 6 The prevalence of thyroid antibodies is approximately 3 to 4 times higher in women compared with men and rise with age. Women aged 44 to 54, 21% to 26% have been found to have thyroid antibodies. 7 The prevalence of overt hypothyroidism also rises with age, particularly in women; coincident with the rise in the prevalence of autoimmune thyroiditis. 8 Subclinical hypothyroidism also predominates in women, occurring in approximately 75% of women and 3% in men. Elderly women are estimated to have up to 16% rate of subclinical hypothyroidism. 9 Hashimotos thyroiditis (chronic lymphocytic thyroiditis) is the most common cause of clinical hypothyroidism in the United States. Other causes include idiopathic atrophy, deficiency of dietary iodine, hypopituitrism, and hypothalamic disease resulting in deficiency TRH production and iatrogenic hypothyroidism (i.e. from medication such as lithium). In patients experiencing a severe medical condition, T 3 level may be low from decreased conversion of T 4 to T 3 a condition known as euthyroid sick syndrome. 10 Symptoms of hypothyroidism tend to manifest once TSH level surpass 8-12 mIU/L and include low energy appetite and sleep change, poor concentration, apathy and lung expanse latency. 11 Other symptoms include cold intolerance, constipation, muscle cramps, parathesis, mental disturbances (amenorrhea or menorrhagea) dyspenia dizziness, syncope, reduced hearing, poor appetite, weight gain, brittle and thinning hair, husky voice, bradycardia, cardiomegaly low voltage complexes on ECG, elevated levels of cholesterol and triglycerides and normochromic, normocytic anemia from a reduced rate of RBC production.

The symptoms of hypothyroidism are correctable with thyroid supplementation but may not resolve until several weeks after the normalization of serum thyroid hormone levels. 12 Exogenous thyroid hormine is administered as L-thyroxin, I-triiodothyronine (Synthetic T 3), preparations of mixed synthetic T 4 and T 3 and desccated thyroid. L-thyroxin and L-triiodothyronine typically range between 25 to 100pgm/day and 12.5 to 50pgm/day respectively.

1 c) Subclinical Hypothyroidism

Subclinical hypothyroidism (SCH) is defined as a serum thyroid-stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxine. Serum TSH has a log-linear relationship with circulating thyroid hormone levels (a 2-fold change in free thyroxine will produce a 100-fold change in TSH). Thus, serum TSH measurement is the necessary test for diagnosis of mild thyroid failure when the peripheral thyroid hormone levels are within normal laboratory range. 13 The individual range for peripheral thyroid hormones is narrower than the population reference laboratory range; therefore, a slight reduction within the normal range will result in elevation of serum TSH above the normal range. Subclinical hypothyroidism or mild thyroid failure is a common problem, with a prevalence of 3% to 8% in the population without known thyroid disease. 14 The prevalence increases with age and is higher in women. After the sixth decade of life, the prevalence in men approaches that of women, with a combined prevalence of 10%. Antithyroid antibodies can be detected in 80% of patients with SCH have a serum TSH of less than 10 mIU/L.

Before diagnosis of SCH, other causes of an elevated TSH level, such as recovery from nonthyroidal illness, assay variability, presence of heterophile antibodies interfering with the SCH assay, and certain cases of central hypothyroidism with biologically inactive TSH and thyroid hormone resistance, should be excluded. However, the most common cause of elevated TSH is autoimmune thyroid disease.Previous radioiodine therapy, thyroid surgery, and external radiation therapy can also result in mild thyroid failure. Transient SCH may occur after episodes of postpartum, silent, and granulomatous thyroiditis. 15 The clinical importance of and therapy for mild elevation of serum TSH (<10 mIU/L)5 and the exact upper limit of normal for the serum TSH level remain subjects of debate. 16 When the TSH is above 10mIU/L, levothyroxine therapy is generally agreed to be appropriate.However, management of patients with a serum TSH level of less than 10 mIU/L is controversial. 17 Some authors argue for routine and some for selective therapy. A recent 2007 meta-analysis of 14 randomized clinical trials enrolling a total of 350 patients concluded that levothyroxine replacement therapy for SCH does not result in improved survival or decreased cardiovascular morbidity.

Data on health-related quality of life and symptoms did not show significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improve some parameters of lipid profiles and left ventricular function. 18 clinical feature of hypothyroidism, but subtle somatic symptoms, cognitive defects have been observed in association with this condition. symptoms include dry skin, cold intolerance, fatigue, alteration in lipid metabolism and cardiac function and lower score on memory tests. These symptoms had improved by thyroid hormone treatment. Approximately 5 to 15% of patients with subclinical hypothyroidism progress to overt hypothyroidism within a year. Patients with any thyroid antibodies are at high risk, 80% progressing to overt hypothyroidism within four years.

2 III. Results

The study sample comprises 118 subjects, fulfilling the inclusion criteria were recruited in the study with their consent. After detailed history and clinical evaluation, blood sample was taken for estimation of various

biochemical parameters in serum namely fT 3 , fT 4 , TSH, Insulin, Triglycerides, HDL-C, and fasting glucose. The results obtained are presented in various tables diagrams.

3 a) Sex Distribution of Metabolic Syndrome

The sex distribution of prevalence of metabolic syndrome is shown in Table 1. The percentage of male and female in metabolic syndrome were 20% and 38.4% respectively of total subjects in the study.

4 c) Distribution of Metabolic Syndrome in Thyroid Groups

Out of total 118 subjects studied 60 were in overt hypothyroid group and 58 in subclinical hypothyroid group. Among these groups metabolic syndrome is almost equally distributed. Similarly male and female subjects were almost equal in both groups with more number of females (n =22 and n = 24) in overt and subclinical hypothyroid groups respectively. Results in Table 2. In overt hypothyroid case fT 3 is negatively correlated with systolic blood pressure, fasting glucose triglyceride level and HDL levels. T 3 negatively correlated with systolic blood pressure and HDL-C level in subclinical hypothyroid group. Results in Table **??** Table **??** was found between fT4 and any of the components of metabolic syndrome. 8. The -HOMA-IR (insulin resistance) is comparable is overt (5.38±3.4) and subclinical hypothyroid (6.27±3.87) groups. Therefore screening and treatment of subclinical hypothyroids may be warranted due to its adverse effect on glucose metabolism Hence the fact that insulin resistance was similar in both thyroid groups where there is significant difference in the levels of thyroid hormones indicate that thyroid hormone per se may not be responsible for this phenomenon. 9. Elevated triglyceride is the most prevalent (81%) component of metabolic syndrome in all thyroid patients of present study. Hence hypertriglyceridemia on routine evaluation may warrants screening for other components of metabolic syndrome. 10. There is a significant correlation (p= 0.03) between waist circumference and triglyceride levels. It is the visceral fat which is responsible for hypertriglyceridemia. Hence it can be concluded that those having high TG levels and high waist circumference, have visceral adiposity. Therefore screening for other parameters of metabolic syndrome may be warranted as visceral adipose tissue causes the most metabolic derangements.

The Various results conclude that a significantly deep association exists between Thyroid dysfunction and Metabolic Syndrome.

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Figure 1: I

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Figure 2: P

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Sex	Metabolic Syndrome	Non Metabolic Syndrome	Total
Male	24 (20%)	19 (16.1%)	43 (36.4%)
Female	45 (38.4%)	30 (25.4%)	75 (63.5%)
Total	69 (58.4%)	49 (41.5%)	118

b) Age Wise Distribution of Metabolic Syndrome
The prevalence of metabolic syndrome is increasing with age with maximum in age group 40-49 years and we can observe that maximum numbers hypothyroid patients are in age group of 30-39 yea with 59% of prevalence of metabolic syndrome.

Figure 3: Table 1 (

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Age classes (years)	All patients (n)	Metabolic Syndrome (n)
20-29	17 (14%)	5 (29%)
30-39	49 (41.5%)	29 (59%)
40-49	22 (18.6%)	16 (72%)
50-59	18 (15%)	7 (38.8%)
60-69	12 (10%)	7 (58.3%)

Figure 4: Table 1 (

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Met syn F 22 F 24 In overt hypothyroid group, both metabolic and Overt Hypothyroid M 12 Subclinical Hypothyroid M 11 Total 69 d) Thyroid Function Test in Metabolic Syndrome non metabolic syndrome group, fT 3 , fT 4 are comparably decreased but TSH is significantly increased in metabolic syndrome group. Global Journal of Non Met Syn Total Total 26 60 34(56%) Total 23 58 35(60%) 49 118

Figure 5: Table 2 :

3

		fT 3	fT 4	TSH
Overt hypothyroid	Non Met Syn	2.4 ± 1.12	6.4 ± 2.14	11.5 ± 4.8
	Met Syn	2.73 ± 1.32	7.30 ± 2.80	14.6 ± 5.42*
Subclinical Hypothyroid	Non Met Syn	5.6 ± 1.12	14.9 ± 2.4	8.24 ± 5.28
	Met Syn	5.1 ± 1.17	16.2 ± 2.8	9.1 ± 5.03

p <0.05

Figure 6: Table 3 :

4

	Overt Hypothyroid		Subclinical Hypothyroid	
	Non Met Syn	Met Syn	Non Met Syn	Met Syn
WC (inch)	32.8 ± 2.5	36.9 ± 3.6	33.3 ± 2.4	37.17 ± 3.12
SBP (mmHg)	127.6 ± 12.7	136.7 ± 17.1	123 ± 11.1	138.4 ± 15.4
DBP(mmHg)	83.9 ± 7.1	89.2 ± 9.7	84 ± 7.3	91.39 ± 10.67
FG(mg/dl)	90.7 ± 16.0	111.8 ± 19.2*	95.2 ± 11.2	136 ± 33.1*
TG(mg/dl)	136.3 ± 33.1	198.1 ± 58.6*	175.2 ± 52	155.29 ± 45.65
HDL(mg/dl)	44.2 ± 8.2	41.9 ± 8.3	44.6 ± 8.8	41.73 ± 8.98

*p<0.05 in comparison to subclinical hypothyroidism by student test

Figure 7: Table 4 :

19.49%

25.42%

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10 38.98%

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WC (inch)	Overt Hypothyroid P value -0.338 r 0.03* -0.008 0.951	
SBP (mmHg)		
DBP(mmHg)		
FG(mg/dl)		
TG(mg/dl)		
HDL-C(mg/dl)	-0.025	0.849

fT 4 is negatively correlated with waist circumference, fasting glucose, triglycerides and HDL levels in overt hypothyroid group. Similarly in subclinical group there is negative correlation with waist circumference and systolic blood pressure. Result in Table 6.

Figure 8: :

6

	Overt Hypothyroid		Subclinical Hypothyroid	
	r	P value	r	P value
WC (inch)	-0.0845	0.518	0.061	0.735
SBP (mmHg)	0.143	3.276	0.137	0.305
DBP(mmHg)	0.063	3.633	3.056	0.675
FG(mg/dl)	-0.069	0.599	0.044	0.743
TG(mg/dl)	-0.046	0.725	5.177	0.184
HDL-C(mg/dl)	-0.192	0.140	0.044	0.743

IV. Summary and Conclusion

1. In the present study females hypothyroid cases have more prevalence of Metabolic syndrome {n=45 (38.4%)}, than male hypothyroid cases {24 (20%)} Hence it will be worthwhile to screen female patients with hypothyroidism, for risk of metabolic syndrome.
2. Highest prevalence of metabolic syndrome in hypothyroid patient was in 40-49 years of age group {total n=22, cases of metabolic syndrome is n=16 (72%)}. This is also the age group where there is highest risk of subclinical hypothyroidism.
3. The prevalence of Metabolic Syndrome is comparable in overt hypothyroid cases {56% (n=34)} and subclinical hypothyroid cases {60% (n=35)}. Hence this warrants the intensive screening of subclinical hypothyroid group.
4. TSH values were high in metabolic syndrome group (14.6 ± 5.42 mIU/L) in comparison to non metabolic syndrome group (11.5±4.8 mIU/L) in both the thyroid groups. Therefore patients with higher TSH in subclinical hypothyroidism are not more risk of developing metabolic syndrome.
5. When components of metabolic syndromes were compared, overt hypothyroid group had significantly elevated triglyceride levels (198.1±58.6 mg/dl) than subclinical hypothyroid group (155.29±45.65 mg/dl) and subclinical hypothyroid group had significantly elevated fasting glucose (136±33.1 mg/dl) as compared to overt hypothyroid group (111.8±19.2 mg/dl). Hence it can be made out that subclinical patents are at higher risk of metabolic syndrome as they also had greater mean of abdominal obesity, and diastolic blood pressure.
6. TSH had significant positive correlation with fasting glucose (r=0.337, p=0.009), diastolic blood pressure (p = 0.049) and triglycerides level (p=0.40) in overt hypothyroid cases. In subclinical cases TSH is negatively correlated with fasting glucose and HDL-C levels and significant positive

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