A Relevance of Lipid Changes in Hypothyroidism Patients Associated with and without Metabolic Syndrome

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ABSTRACT

Introduction: Thyroid hormones appear to serve as a general pacemaker accelerating metabolic process and may be associated with metabolic syndrome. Metabolic syndrome (MetS), a cluster of disorders including central obesity, glucose intolerance, hypertension and dyslipidemia, has been used to identify individuals at risk of cardiovascular disease (CVD).

Material and Methods: A total of 81(cases 51, control 30) hypothyroid patients with age and gender matched were recruited as control group. Lipid profile and thyroid profile were investigated by using standard procedures.

Results: Lipid profile consisted of TC, TG, VLDL-C, LDL-C and ratios of TC/HDL-C and LDL-C/HDL-C showed statistical significantly raised (P <0.0001) whereas HDL-C observed decreased (P <0.0001) as same manner in total hypothyroid patients than control group. In case of thyroid profile T3 and T4 showed statistical significantly decreased as HDL-C (P<0.0001) while TSH levels found significantly higher in hypothyroid patients than control group. The significant changes were found in some variable on comparison between with and without metabolic syndrome groups of subclinical and overt hypothyroidism patients.

Conclusion: This study on metabolic syndrome in thyroid dysfunction population may help us to plan management strategies, resulting in significant reduction in cardiovascular morbidity and mortality due to metabolic syndrome.

Keywords: Hypothyroidism, Metabolic Syndrome, Lipid Profile and Thyroid Profile

INTRODUCTION

Hypothyroidism is a very common endocrine problem; it causes symptoms that reduce the functional status and quality of life. Hypothyroidism is defined as a deficiency of thyroid activity. It results from reduced secretion of either total thyroxine (T4) or triiodothyronine (T3). It leads to hyper-secretion of pituitary thyroid-stimulating hormone (TSH) and so greater increase in serum TSH levels.[1] Hypothyroidism can be either overt or subclinical. Subclinical hypothyroidism predisposes to overt hypothyroidism. Hypothyroidism leads to hypercholesterolaemia because of reduced activity of lipoprotein lipase and thus increases the cardiovascular risk.[2] Thyroid hormones appear to serve as a general pacemaker accelerating metabolic process and may be associated with metabolic syndrome.[3] Metabolic syndrome (MetS), a cluster of disorders including central obesity, glucose intolerance, hypertension and dyslipidemia, has been used to identify individuals at risk of cardiovascular disease (CVD)[4,5] Thyroid functions affect metabolic syndrome parameters including HDL cholesterol, triglycerides, blood pressure and plasma glucose. Thyroid dysfunction is a risk factor for CVD mediated by the effects of thyroid hormones on lipid metabolism and blood pressure.[6]

Criteria to definition of metabolic syndrome (MetS)

The metabolic syndrome criteria according to the 2001 National Cholesterol Education Program/ATP III[4]: Current ATP III criteria define the metabolic syndrome as the presence of any three of the following five traits:

1. Abdominal obesity, defined as a waist circumference in men >102 cm (40 in) and in women >88 cm (35 in). 2. Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides. 3. Serum HDL cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C. 4. Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure. 5. Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

This study was carried out to find out the relationship in changes of lipids levels in hypothyroid patients with and without metabolic syndrome and to see the correlation of different components of lipid profile with TSH levels.

MATERIAL AND METHODS

The study was performed in Clinical Biochemistry Department, Sri Aurobindo Institute of Medical Sciences, Indore. A total of 81(cases 51, control 30) hypothyroid patients with age and gender matched were recruited as control group by using convenience sampling technique. After obtaining the informed consent each patient was subjected to detailed history and clinical examination which include anthropometric measurements, lipid profile and thyroid profile. On this basis only those patients were selected who were having hypothyroidism with or without metabolic syndrome. Subjects were taking lipid lowering drugs, pregnant women and infants were excluded as cases from the study. Healthy age and gender matched controls with no acute or chronic illness, on anti-inflammatory drugs, pregnant women or women using

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oral contraceptive pills were excluded as controls. Serum Total T3, Total T4 and TSH were analyzed on fully automated immunoassay system (Cobas e411, Roche, Hitachi) based on principle of chemiluminiscence immunoassay. Lipid profile included measurement of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were analyzed by Vitros-5.1, FS auto analyzer by using ready-made dry chemistry kits from Ortho-Clinical diagnostics, Johnson & Johnson, USA. Low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) calculated by using the Friedwald formula. The data was analyzed by using XLSATE version 2014 software package. Mean, Standard deviation and correlation coefficient (r) were applied. A *P* value < 0.05 was considered as statistically significant.

RESULTS

The present work is a hospital based cohort study in which 51 hypothyroid subjects, with or without metabolic syndrome, were recruited. Of the 51 hypothyroid patients with mean age of 38.92 ± 11.27 years, 31 were females and 20 were males in the study group. Patients were distributed in to different groups. The percentage of hypothyroidism and metabolic syndrome in each group were determined.

Out of total 51 subjects 22 were overt hypothyroid and 29 in subclinical hypothyroid group. Among these groups MetS is distributed, 58.8 % in overt hypothyroidism and 41.3% in subclinical hypothyroidism. Whereas more number of females (n=11 and n=9) in overt and subclinical hypothyroid groups than male (n=7 and n=3). Our study revealed that the prevalence of metabolic syndrome was more among the females with thyroid dysfunction. This conclusion was withdrawn from: 75% of SCH and 61.1% of overt hypothyroid patients were females and that metabolic syndrome is significantly higher in SCH and overt hypothyroidism patient group. A higher prevalence in women might be related to their higher rate of obesity. In the present study we found the extremely significantly (*P* <0.0001) increased of all anthropometric parameters (blood pressure, BMI and WC) except age (p=0.1738 NS) in total (n=51) hypothyroidism patients than control (n=30) subjects. Lipid profile consisted of TC, TG, VLDL-C, LDL-C and ratios of TC/HDL-C and LDL-C/HDL-C showed statistical significantly raised (*P* <0.0001) whereas HDL-C observed decreased (*P* <0.0001) as same manner in total hypothyroid patients than control group. In case of thyroid profile T3 and T4 showed statistical significantly decreased as HDL-C (*P* <0.0001) while TSH levels found significantly higher in hypothyroid patients than control group. (Table 1). In the present work we did not find any statistical significant (*P* >0.05) difference in age between any group.

Table 2 showed the significance changes between overt and subclinical hypothyroidism patients.

Lipid profile and TSH levels showed the statistical significantly higher (*P* <0.001) while T3, T4 and HDL-C showed significantly decreased (*P* <0.001) in overt hypo when compared with SCH patient. No significant differences were found in anthropometric parameters (Age, WC, BMI and blood pressure) with *P* values 0.3487, 0.1186, 0.3618 and 0.3108 respectively between overt and subclinical hypothyroidism patients. Whereas all variables were found significantly (*P* <0.001) elevated except age while T3, T4 and HDL-C were observed (*P* <0.001) significantly lower in both the groups when they compared with control group.

In the present work, we did not find any significant changes on comparison between with and without metabolic syndrome groups of overt hypothyroidism patients. All variable

Parameters	Hypothyroidism (Mean±sd)	Control (Mean±sd)	*P* values
Age (Years)	38.92±11.27	36.70±8.08	0.1738
WC (CM)	93.88±7.75	80.16±4.04	<0.0001
BMI (Kg/M^2)	26.33±1.48	23.00±1.12	<0.0001
BPS (MM/Hg)	126.17±7.97	118.16±4.37	<0.0001
DPS (MM/Hg)	87.78±6.06	80.16±4.04	<0.0001
TC (MG/DL)	190.08±57.46	116.42±13.74	<0.0001
TG (MG/DL)	174.55±52.53	102.57±10.14	<0.0001
HDL-C (MG/DL)	28.42±5.59	47.90±5.22	<0.0001
LDL-C (MG/DL)	126.69±56.79	48.01±14.97	<0.0001
VLDL-C (MG/DL)	34.91±10.50	20.51±2.02	<0.0001
TC:HDL-C	7.27±3.72	2.46±0.44	<0.0001
LDL-C:HDL-C	4.97±3.26	1.02±0.40	<0.0001
T3 ng/ML	0.93±0.42	1.67±0.27	<0.0001
T4 µg/ML	5.03±2.08	9.69±1.05	<0.0001
TSH µIU/ML	35.81±31.69	3.59±0.98	<0.0001

All values are expressed in mean & standard deviation (Mean±SD).
P values less than 0.05 indicates significant difference between the two groups or variables.
Abbreviation: BMI=body mass index; BPS=systolic blood pressure; DPS=diastolic blood pressure; WC= waist circumference; T3=t-riiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone HDL-C=high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; TC=total cholesterol; TG=triglyceride; TC: HDL= ratio of total and high density lipoprotein cholesterol; LDL:HDL= ratio of low density lipoprotein and high density lipoprotein cholesterol.

Table-1: Comparison of all variables between Control and Hypothyroidism Subjects

reported statistical not (P >0.05) significant. Only Age, diastolic blood pressure, WC, BMI, HDL-C and TSH levels considered not but quit significant with P values 0.0962, 0.0698, 0.0524, 0.0744, 0.0692 and 0.0512 respectively. But when they compared with control subjects some of variables showed significant variation. Overt hypothyroidism with metabolic syndrome group presented the extremely significantly (P <0.0001) raised values of all variables except T3,T4 and HDL-C which were showed significantly decreased on comparison with control group whereas without metabolic syndrome group showed the extremely (P <0.0001) significantly increased of BMI, lipid profile, TSH and systolic blood pressure showed statistical significant (P =0.0325) while T3, T4 and HDL-C observed significantly decreased and diastolic blood pressure considered not quit significant with P =0.0560 on comparison with control group. (Table 3). The significant changes were found in some variable on comparison between with and without metabolic syndrome groups of subclinical hypothyroidism patients. Thyroid profile (T3, T4 and TSH) and diastolic blood pressure reported not (P >0.05) significant. BMI and lipid profile except HDL-C showed the significantly (p<0.001) higher and HDL-C declined (P <0.001) significantly in SCH with MetS than without MetS of SCH group. Whereas TG and VLDL observed not statistical (P >0.05) significant with P values 0.4711 while Age and systolic blood pressure considered not quit significant with P values 0.0793 and 0.0870 respectively. (Table 3).

But when they compared with control group we noticed the extremely significantly changes in all variables except age. Subclinical hypothyroidism with and without metabolic syndrome group showed the extremely significant (P <0.0001) difference with all variables except age (P =0.3531, 0.1553) on comparison with control group. (Table 3).

We also compared between with and without metabolic syndrome groups of both overt and subclinical hypothyroidism. The measured anthropometric (age, blood pressure, WC and BMI) parameters found not significant (P >0.05) while HDL considered not quit significant with P values 0.0887 and rest of the variables (TC, TG, LDL, VLDL, TC:HDL, LDL:H-

Parameters	Overt hypothyroidism (Mean±sd)	Subclinical hypothtroidism (Mean±sd)	P values
Age (Years)	39.63±9.96	38.37±12.30	0.3487
WC (CM)	95.36±9.43	92.73±6.13	0.1186
BMI (Kg/M^2)	26.42±1.76	26.27±1.25	0.3618
BPS (MM/Hg)	126.81±7.95	125.68±8.09	0.3108
DPS (MM/Hg)	87.95±6.66	87.65±5.68	0.4317
TC (MG/DL)	224.41±67.69	164.03±28.83	<0.0001
TG (MG/DL)	204.60±60.75	151.57±30.20	<0.0001
HDL-C (MG/DL)	25.81±5.22	30.48±5.06	0.0012
LDL-C (MG/DL)	157.67±67.89	103.20±31.26	0.0002
VLDL-C (MG/DL)	40.92±12.15	30.35±6.04	<0.0001
TC:HDL-C	9.43±4.47	5.64±1.81	<0.0001
LDL-C:HDL-C	6.76±3.98	3.62±1.64	0.0002
T3 ng/ML	0.60±0.34	1.18±0.28	<0.0001
T4 µg/ML	2.96±1.11	6.61±0.93	<0.0001
TSH µIU/ML	60.11±33.10	17.37±12.47	<0.0001

Table-2: Comparison of all Variables between all three Study Groups

Parameters	Overt Hypothyroidism (Mean±sd)		Subclinical hypothtroidism (Mean±sd)	
	With MetS	Without MetS	With MetS	Without MetS
Age (Years)	39.31±9.46	32.75±1.70	42.25±13.71	35.64±10.81
WC (CM)	96.20±9.40	87.63±6.39	94.61±7.27	91.44±5.00
BMI (Kg/M^2)	26.63±1.78	25.15±1.61	26.82±1.32	25.88±1.08
BPS (MM/Hg)	128.43±8.70	122.50±2.08	128.33±9.12	123.82±6.96
DPS (MM/Hg)	89.37±6.80	83.75±6.39	88.50±6.65	87.05±5.01
TC (MG/DL)	234.19±63.34	186.50±96.07	182.75±21.63	150.82±26.17
TG (MG/DL)	211.58±668.42	175.25±21.68	152.25±29.16	151.40±31.79
HDL-C (MG/DL)	25.37±4.48	29.75±7.22	27.50±3.26	32.58±5.11
LDL-C (MG/DL)	166.50±62.71	121.70±99.02	124.80±21.34	87.95±28.30
VLDL-C (MG/DL)	42.31±13.68	35.05±4.33	30.45±5.83	30.28±6.36
TC:HDL-C	9.88±4.57	7.07±4.77	6.77±1.39	4.83±1.66
LDL-C:HDL-C	7.14±4.03	4.79±4.40	4.65±1.25	2.88±1.51
T3 ng/ML	0.57±0.35	0.68±0.39	1.10±0.25	1.24±0.29
T4 µg/ML	2.81±10.5	3.14±1.55	6.75±0.95	6.51±0.93
TSH µIU/ML	68.13±32.44	36.71±33.67	20.59±16.68	15.10±8.22

Table-3: Comparison of all Variables between all Study Groups

DL, T3, T4 and TSH) showed highly significant (P <0.001) between overt and subclinical with metabolic syndrome patients group. Only the thyroid profile (T3, T4 and TSH) showed the significant (P <0.001) difference while TC, TG, VLDL, and ratio of TC:HDL and LDL:HDL considered not but quit significant with P values 0.0854, 0.0873, 0.0873, 0.099 and 0.0705 respectively and rest of the variables (age, blood pressure, WC and BMI) reported not (P >0.05) significant on comparison without metabolic syndrome of overt and subclinical patients groups. (Table 3).

In the present work we measured the correlation coefficient (r) between TSH and other investigated variables in total hypothyroidism patients. We observed the direct relationship between TSH and most of the variables. TC, LDL-C, VLDL-C TG including ratios of TC/HDL-C and LDL-C/HDL-C showed the positive relationship with TSH levels. (Table 4). Out of the anthropometric parameters only the BMI showed positive whereas age and BP did not show any significant relation to the TSH while WC considered not quit significant. We also observed an inverse relationship between TSH and thyroid hormone (T3 and T4) and HDL-C levels in total hypothyroidism patients.

S. No.	Parameters	Correlation coefficient (r)	P values
	AGE (Years)	0.001	0.9905
	WC (CM)	0.2573	0.0684
	BMI (Kg/M^2)	0.3044	0.0299
	BPS (MM/Hg)	0.0497	0.7288
	DPS (MM/Hg)	0.0726	0.6124
	TC (MG/DL)	0.6221	<0.0001
	TG (MG/DL)	0.6774	<0.0001
	HDL-C (MG/DL)	-0.4318	0.0016
	LDL-C (MG/DL)	0.5466	<0.0001
	VLDL-C (MG/DL)	0.6774	<0.0001
	TC:HDL-C	0.5591	<0.0001
	LDL-C:HDL-C	0.5173	<0.0001
	T3 ng/ML	-0.8302	<0.0001
	T4 µg/ML	-0.7069	<0.0001

r=correlation coefficient between the variables; P values less than 0.05 indicates significant difference between the two groups or variables.

Table-4: Correlation between TSH and all Variables in Total Hypothyroidism Patients

DISCUSSION

Hypothyroidism is associated with many biochemical abnormalities. Levels of total cholesterol and low density lipoprotein cholesterol tend to increase as thyroid function declines.[7] Thus hypothyroidism constitutes a significant cause of secondary dyslipidemia. Jung[8] found mean plasma total cholesterol and LDL cholesterol levels elevated in hypothyroidism cases than normal controls. In another study, average serum total cholesterol level was found elevated in primary and secondary hypothyroidism.[9] Keyes and Heimberg[10], Laker and Mayes[11] found triglyceride level elevated in hypothyroid patients. So, our study findings were consistent with the previous studies done by other investigators.

In hypothyroid patients, despite the reduced activity of HMG CoA reductase, there is often an increase in the serum total cholesterol concentration, mainly due to raised levels of serum LDL cholesterol and intermediate density lipoprotein (IDL) cholesterol.[12] Decreased thyroid secretion greatly increases the plasma concentration of cholesterol because of decreased rate of cholesterol secretion in the bile and consequent diminished loss in the feces due to decreased number of low density lipoprotein receptors on liver cells.[13] Decreased activity of LDL receptors resulting in decreased receptor-mediated catabolism of LDL and IDL is the main cause of the hypercholesterolemia observed in hypothyroidism.[14]

Increase in HDL cholesterol concentration is mainly due to increased concentration of HDL2 particles. Dullaart[15] have stated that decreased activity of CETP (cholesteryl ester transport protein) results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL cholesterol levels. Lam[16] have stated that in hypothyroid patients decreased activity of hepatic lipase leads to the decreased catabolism of HDL2 particles leading to increased HDL. So, decrease in HDL cholesterol level in our study might be due to increased activity of CETP and lipoprotein lipase in hypothyroid patients.

Our study also revealed the prevalence of metabolic syndrome was more among the females with thyroid dysfunction. A higher prevalence in women might be related to their higher rate of obesity. This finding was consistent with the study done by Shantha et al.,[17] who found that females with metabolic syndrome had significant association with SCH. The study by Uzunlulu et al;[18] and Nehal Hamdy et.al;[19] had also shown females to be more associated with SCH and metabolic syndrome.

Our study was similar to other authors who were reported as patients with overt hypothyroidism exhibit significantly higher TC, LDL-C and TG compared to normal controls.[20] The increase in lipid levels can be reversed by thyroid hormone supplementation.[21] In subjects with subclinical hypothyroidism, significant increase in the levels of TC, LDL-C, TC/HDL ratio compared to euthyroid subjects has been also observed.[22] The significant and independent relationship between TSH and TG, as shown in the current study was further supported by the observations of Wang et al.[23], in which TSH and TG was significantly associated in a Chinese euthyroid population. They also found that TSH was not associated with HDL-C and LDL-C which were not similar to the present study. We reported significantly higher values in lipid and BMI in with metabolic syndrome than without metabolic syndrome cases of subclinical hypothyroidism patients. Whereas Lai Y et. al., have been suggested an associations between subclinical thyroid disease and MetS in their previous studies. A recent study in Taiwan explored the relationship between serum TSH levels and components of MetS, concluding that even slight increases in TSH, as in subclinical hypothyroidism, may be a MetS risk factor; in that study, TSH levels were significantly higher in the MetS group than in the non-MetS group.[24]

In our study showed the positive relationship of high TSH with BMI in total hypothyroidism patients while according to Roos *et al* study's[6] showed positive relationship of low T3 and T4 with WC in both men and women. Some studies showed adipocytes and pre-adipocytes expressed TSH receptors, TSH bounded with TSH receptors and induced pre-adipocytes to produce and release adipokines, some of them such as leptin played a very important role in the onset of metabolic syndrome and cardiovascular disease.[25] Abnormal thyroid function can increase peripheral vascular resistance and activate the sympatho-adrenal system, leading to increase in BP but our findings are in disagreement with some researchers like Salkiti et al[26], Waterhouse et al[27] and Nagasaki et al[28] who found that TSH positively correlated with systolic BP and or diastolic BP. Park et al[29] found that higher levels of TSH predict the prevalence and risk of metabolic syndrome in overt hypothyroidism and subclinical hypothyroidism. We also agreed with their study. Our study has confirmed the presence of a positive relationship between serum TSH and cholesterol levels. This is supported by Xu *et al*.,[30], studies who reported an inverse relationship between thyroxin and cholesterol while the positive with TSH.

CONCLUSION

TSH may be one of many biochemical modulators of circulatory lipids. High TSH was associated with deleterious changes in serum lipids which may increase the cardiovascular mortality and morbidity in patients of subclinical and overt hypothyroidism with metabolic syndrome or without metabolic syndrome. This study on metabolic syndrome in thyroid dysfunction population may help us to plan management strategies, resulting in significant reduction in cardiovascular morbidity and mortality due to metabolic syndrome.

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