Atherogenic Indices- The Risk Indicators in Hypothyroidism?

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

ABSTRACT
Background- The silent spread of hypothyroidism in the general population is on the rise. The adverse effects of long standing hypothyroidism on lipid profile are already known. Some studies suggest that lipoprotein ratios have better predictive capacity on cardiovascular risk factors than individual lipid parameters. The present study paves the way to understand the effects of newly detected hypothyroidism on lipid profile and the importance of Atherogenic indices in predicting complications.
Materials and Methods- This descriptive cross-sectional study was done in 60 hypothyroid patients of 18-45 years age, both males and females, who were either newly detected or on treatment for less than 6 months. Patients with history of other systemic diseases, pregnancy and hyperthyroidism were excluded. After obtaining approval from Institutional Ethics Committee, the patients were selected and informed written consent was taken. Clinical examination was done and blood tests were done for lipid profile.
Results- Statistical analysis was done by Student t-test, ANOVA and Pearson's correlation test. Total cholesterol, LDL and Non HDL showed significant variations among different age groups of study population. Atherogenic indices like Total cholesterol/HDL, LDL/HDL and TG/HDL showed significant changes among males and females.
Conclusion- Individual parameters of lipid profile didn't show much change in newly detected hypothyroid patients. But atherogenic indices varied among different age groups and gender. Non HDL had significant variation in the study population (p value-0.0004).This shows the importance of early detection of dyslipidemia and the use of atherogenic indices in hypothyroidism.

Keywords: Age, Atherogenic, Hypothyroidism, Lipid

INTRODUCTION

As the human lifestyle changes, thyroid disorders, cardiovascular diseases, hypertension, joint diseases and overweight are encountered. Thyroid, being a master metabolic gland in our body, has gained much attention in this scenario. One third of the world's population resides in iodine deficient areas and more thyroid diseases are reported from South-East Asia, Latin America and Central Africa. The reports reveal that 300 million of them are suffering from thyroid disease [1], of which, hypothyroidism is common.

Prevalence of hypothyroidism in India is 11% when compared to 2% in United Kingdom and 4.6% in United States of America [2]. Thyroid hormones have effects on growth, metabolism of carbohydrates, proteins and fats. They increase oxygen consumption and metabolic rate. The impact of hypothyroidism on lipid metabolism is mostly unfavourable, which includes mobilization of triglycerides from the adipose tissue causing increased concentration of free fatty acids in plasma. There is an increase in serum

total cholesterol (TC), Low Density Lipoproptein cholesterol (LDL-C), Apolipoprotein B, Lipoprotein (a) levels and possibly triglyceride (TG) levels [3]. In previous years, Low Density Lipoprotein cholesterol was considered as the main index for cardiovascular disease and target for therapy. Since the amount of LDL-cholesterol inside the lipoprotein particle varies in individuals, its measurement does not reflect the number of particles and therefore the true level of cardiovascular risk. Researchers found that the more precise way to determine risk would be to measure the number of Atherogenic lipoprotein particles in the serum that is apolipoprotein-B [4]. So for the optimization of predictive capacity of lipid profile, the lipoprotein ratios are being used nowadays which correlate with the size and composition of lipoproteins. They are generally referred to as 'Atherogenic Indices', which are the better reflection of metabolic and clinical interactions between lipid parameters [5]. This study summarizes the rationale of using the indices as the predictive measure for the diagnosis of early complications in hypothyroidism on lipid profile.

MATERIALS AND METHODS

The present study was done in a tertiary care center. Protocol of the study was approved by Institutional Ethics Committee (45/14/IEC/JMMC & RI). Data was collected from 60 hypothyroid patients, attending the Endocrinology out-patient department, both males and females of 18-45 years, who were newly detected or on treatment for less than 6 months. Patients with Hyperthyroidism, COPD, history of smoking, Heart diseases, Diabetes Mellitus and Pregnancy were excluded. For Lipid Profile, blood

tests were done and from the results, Atherogenic indices were calculated. The parameters considered were Total Cholesterol/HDL (Coronary Risk Index), LDL/HDL, TG/HDL and Non- HDL cholesterol. They are useful for the assessment of cardiovascular risk [6]. The patients were divided on the basis of risks assessed by Atherogenic indices as follows:-

  a. **Total cholesterol/HDL ratio-**Ideal<3.5, Moderate risk 3.5-5,High risk >5
  b. **LDL/HDL ratio-** Ideal <2.5, Moderate risk 2.5-3.3, High risk >3.3
  c. **TG/HDL ratio-**Ideal <2, Moderate risk 2-3.8, High risk > 3.8
  d. **Non HDL cholesterol-** Non HDL cholesterol is total cholesterol minus HDL cholesterol which represents the measurement of cholesterol in LDL, IDL and VLDL particles. It is gaining importance nowadays as a good predictor of cardiovascular risk. Ideal <130 mg/ dl, Moderate risk 130-159 mg/ dl, High risk is >159 mg/dl.

Statistical analysis was done by Student t-test, ANOVA and Pearson's correlation test.

RESULTS

Based on the inclusion and exclusion criteria, 60 hypothyroid patients were included in the study. Of this, 49 were females and 11 were males.TSH value of >4.25 m IU/L was considered as Hypothyroidism and mean TSH value of the present study group was 26.87 ± 39.58 (standard error is 5.11). Of the 60 patients included in the study, 65% had positive family history and 35% had negative. The mean duration of illness was 3.13 ± 1.54 months.

Table 1: Demographic profile of study group

Variables	Mean± SD
Age (years)	35.75± 7.3
Height(cm)	159.3± 6.58
Weight (kg)	70.63 ± 14.6
BMI (kg/m^2)	27.71 ± 5.05

On analyzing the lipid profile of the hypothyroid patients, it was found that 42% had high cholesterol with mean value of 227.04± 22.52. LDL cholesterol

had high values for 18% people with mean value 157.81 ±10.98. Only 5% patients had high VLDL level with the mean value of 73.33± 43.66. Low HDL

was found in 17% patients with mean value of 34.9±4.4. 17% had high TG levels with mean value of 179.3±35.82. The variation of lipid profile among different age groups was significant for total cholesterol (p value-0.003) and LDL (p value-0.004). The correlations of total cholesterol and LDL with age groups were also significant. Serum cholesterol, LDL, VLDL and triglyceride were higher in males and HDL was lower, which clearly indicate cardiovascular risk being higher for males compared to females in hypothyroidism. Endogenous oestrogen gives the protective effect on females. Due to the effect of oestrogen, apo-A1 is produced more in females which are the apoproteins of HDL cholesterol. But the variations for lipid profile were not significant among different genders and among different BMI groups [7, 8].

Table 2: Atherogenic Indices of hypothyroid patients

Parameters	Mean ±SD
Total cholesterol/HDL	3.73±1.23
LDL/HDL	2.15±1.04
TG/HDL	2.43±1.09
Non HDL	135.67±36.36

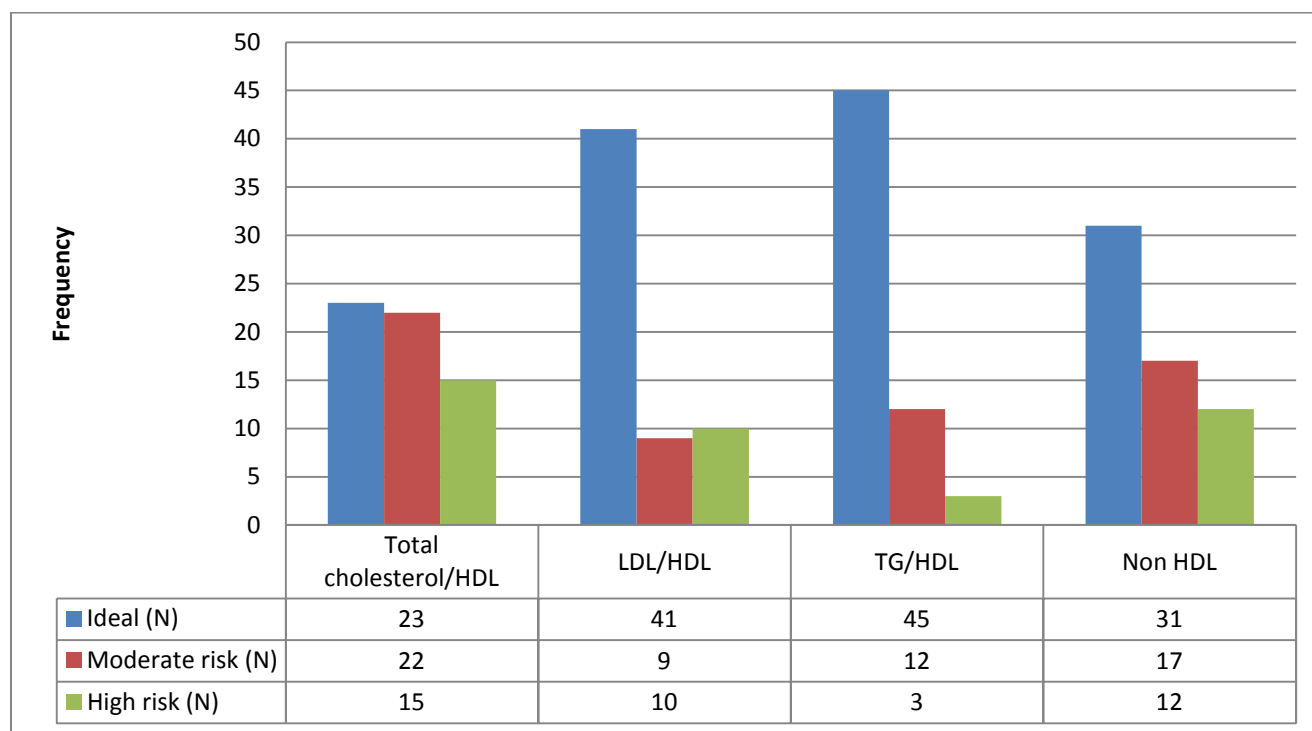|	Total cholesterol/HDL	LDL/HDL	TG/HDL	Non HDL
Ideal (N)	23	41	45	31
Moderate risk (N)	22	9	12	17
High risk (N)	15	10	3	12

Figure 1: Distribution of hypothyroid patients on the basis of risk analysis by Atherogenic indices

Based on the risk for cardiovascular diseases, patients were grouped into ideal, moderate risk and high risk. The mean value of Total Cholesterol/HDL in 23 patients with ideal value was 2.58±0.46, 22 moderate risk was 3.78±0.49 and with 15 high risk was 5.4±0.74. There were 41 patients with ideal LDL/HDL values (1.58±0.58), 9 with moderate risk (2.85±0.21) and 10 with high risk (3.89±0.48). TG/HDL ratio was ideal for 45 patients (1.92±0.51), moderate risk for 12 patients (3.52±0.35) and high risk for 3patients (5.6±1.04).These three ratios were analyzed by ANOVA test between these groups and no statistical significance obtained. Non HDL was ideal for 31 patients (108.32±20.7), moderate risk for

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17 patients (146.5±8.32) and high risk for 12 patients (190.9±14.22). ANOVA test between ideal, moderate risk and high risk groups of Non HDL cholesterol was highly significant (p value -0.004**) .We can conclude that newly detected hypothyroid patients are at moderate cardiovascular risk.

Table 3: Variation of Atherogenic indices with age groups

Parameters	Age groups			P value
	18-25	26-35	36-45	
Total cholesterol/HDL	3.47 ± 1.17	3.53 ± 1.32	3.96± 1.17	0.390
LDL/HDL	2.07±1.06	1.96± 1.11	2.35± 0.98	0.392
TG/HDL	1.89± 0.77	2.56 ± 1.40	2.43 ± 0.83	0.416
Non HDL	120.67±42.94	121.24±30.23	151.2±34.48	0.004**

* p value <0.05- significant, **p value <0.01- highly significant

Table 4: Variation of Atherogenic indices with gender

Parameters	Gender	Mean± SD	P value
Total cholesterol/ HDL	Male	4.51± 1.47	0.019*
	Female	3.55± 1.11	
LDL/ HDL	Male	2.74± 1.18	0.039*
	Female	2.03± 0.98	
TG/HDL	Male	3.21± 1.69	0.008**
	Female	2.25± 0.84	
Non HDL	Male	147± 32.58	0.256
	Female	133.12± 36.9	

* p value <0.05- significant, **p value <0.01- highly significant

No significant variation was obtained for Atherogenic indices among different BMI groups.

DISCUSSION

Even though Hypothyroidism is a genetic disorder, the derangements in lipid parameters are the result of varying lifestyles and inadequate treatment among these patients. Most of the patients had lipid profile in the normal range which may be due to the delayed appearance of cardiovascular symptoms and signs in newly detected and those on treatment for less than 6 months [9]. Changes in thyroid hormones affect the synthesis, digestion, absorption and catabolism of lipids. In hypothyroidism, conversion of cholesterol to bile acids is reduced because, the enzyme Cholesterol-7α hydroxylase (CYP 7A1) is reduced. Mobilisation of fat from the tissues and thus the oxidation of fatty acids are decreased, the actions of lipoprotein lipase is reduced in hypothyroidism so

that triglyceride and VLDL levels are raised. LDL receptor expression is impaired leading to raised LDL levels. This produces Lipoprotein-a, forming 'foam cells' which causes atherogenesis and thrombogenesis. Cholesteryl ester transfer protein (CETP) levels are reduced so that HDL levels are raised [10].

The predictive capacity of lipid profile is limited. Instead, researchers suggest cholesterol ratios as cornerstone of predicting the cardiovascular risk. They are good markers for metabolic and clinical interactions between lipid fractions. Two important components are Total cholesterol/HDL ratio (Castelli Index or Coronary Risk Index) and LDL/HDL ratio because Total cholesterol and LDL specifically, are atherogenic markers having high importance [11].

TG/HDL ratio shows the relationship between atherogenic and protective lipoproteins and reflects the plasma atherogenicity. Non HDL characterizes the measure of cholesterol in LDL, IDL and VLDL particles. In hypertriglyceridemia, it is a secondary therapeutic target [12, 13]. In the Physicians' health study, each unit increase in Total cholesterol/HDL ratio shows 53% increase in the risk of myocardial infarction [14].This is further supported by Coronary Primary Prevention Trial data. This emphasizes the importance of LDL/HDL ratio and Total cholesterol/HDL ratio [15].

Results of the present study show that there is moderate risk of cardiovascular diseases for newly detected hypothyroid patients. Total cholesterol/HDL ratio showed increased results as age advances. So aging is an important predictor of cardiovascular risk in hypothyroidism. Mean value for Non HDL cholesterol showed high significance in comparison between the groups (p value-0.004). Total cholesterol/HDL, LDL/HDL and TG/HDL showed high values in males compared to females, which were statistically significant. Even though Non HDL cholesterol values were high in males, the difference was not significant. It has been recommended to use the ratios in daily clinical life because it gives a clear idea of Atherogenic risk factors and effectiveness of treatment.

CONCLUSIONS

Atherosclerosis is one of the leading causes of morbidity and mortality in the world. It has a long period of silent, slowly progressing episode and one of the main causes for its fast progression is untreated hypothyroidism. The results of this study help to implement a new strategy in identification of hypothyroid patients at risk of deranged lipid profile using Atherogenic indices [16]. Correct diagnosis and timely intervention can prevent the cardiovascular complications. Early levothyroxine supplementation can reverse the changes due to hypothyroidism and prevent further complications, if the patient is committed to the treatment [17].

ACKNOWLEDGEMENTS

Conflicts of interest- Nil

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TABLES AND FIGURES

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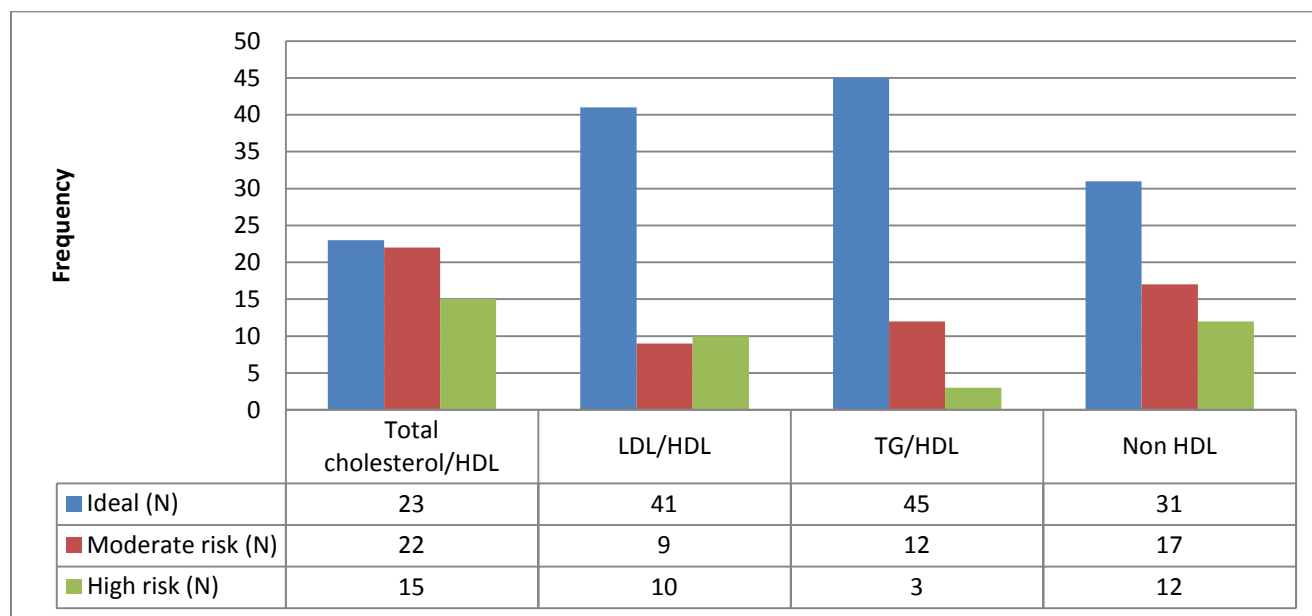|	Total cholesterol/HDL	LDL/HDL	TG/HDL	Non HDL
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ABBREVIATIONS

BMI	-	Body Mass Index
TSH	-	Thyroid Stimulating Hormone
HDL	-	High Density Lipoportein
LDL	-	Low Density Lipoprotein
VLDL	-	Very Low Density Lipoprotein
TG	–	Triglycerides