A HOSPITAL-BASED STUDY OF DYSLIPIDEMIA IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Overt hypothyroidism usually leads to dyslipidemia. The relationship between overt hypothyroidism and dyslipidemia is well established, to that of subclinical hypothyroidism is controversial. Also, Subclinical hypothyroidism if untreated can lead to overt hypothyroidism. So, the present study was conducted to investigate dyslipidema in patients with subclinical hypothyroidism. The study population comprised of total 111 cases having subclinical hypothyroidism and 111 cases of healthy controls. Those with normal T3 and T4 with thyroid stimulating hormone above 4.68 IU/ml were considered subclinical hypothyroidism and were further evaluated for lipid profile. Highest number of participants in the cases belonged to age group 60-71 (36.0%) whereas in control group it was 40-49 years (32.4%). No significant differences were found between lipid parameters between case and control (p >0.05). Serum triglyceride, high density lipoprotein, very low-density lipoprotein was positively correlated with thyroid stimulating hormone (r=0.152, r=0.056, r=0.152, respectively and p=0.110, p=0.560, p=0.110, respectively) whereas total cholesterol, low density lipoprotein was negatively correlated with thyroid stimulating hormone in the cases (r=-0.089, r=-0.118, respectively) and the relation was not statistically significant (p=0.351, p=0.216, respectively). Among control group, serum total cholesterol, high density lipoprotein, low density lipoprotein were positively correlated with thyroid stimulating hormone (r=0.197, r=0.196, r=0.132, respectively) whereas triglyceride, very low density lipoprotein were negatively correlated with thyroid stimulating hormone (r=-0.009, r=-0.025, respectively). Subclinical hypothyroidism may or may not lead to dyslipidemia. Even euthyroid group can have lipid abnormalities. So, screening for hyperlipidemia in general population is more useful rather than patients with subclinical hypothyroidism.

KEYWORDS

Overt hypothyroidism, SCH, dyslipidemia, thyroid dysfunction

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INTRODUCTION

Thyroid hormone mainly affects lipid metabolism by enhancing the utilization, synthesis, and mobilization of triglyceride (TG) from adipose tissue. This will increase the concentration of non-esterified fatty acids (NEFA) and can cause hypertriglyceridemia.[1] Thyroid hormone normally increases the expression of low-density lipoprotein (LDL) receptor and 7 alpha-hydroxylase activity. Hence in case of hypothyroidism, there is downregulation of hepatic LDL receptors which in turn decreases the fractional clearance of LDL and this leads to an increase in LDL cholesterol level. Also, thyroid-stimulating hormone (TSH) level induces the hepatic expression of hydroxymethyl glutaryl CoA (HMG-CoA) reductase which will increase cholesterol synthesis contributing to hypercholesterolemia.[2] Thus, thyroid dysfunction is associated with dyslipidemia.

Thyroid dysfunction is the second most common endocrine condition after diabetes mellitus (DM) and it can be of two types: Hypothyroidism and hyperthyroidism. Hypothyroidism is more common than hyperthyroidism and it is eight times more common in women than in men.[3] About 300 million people worldwide have been discovered to have thyroid-related disorders and over half of them are clueless about their condition.

Hypothyroidism can be of two types, overt and subclinical. Overt hypothyroidism (OH) means reduced secretion of both thyroxine (T4) and triiodothyronine (T3) and this decrease in T4 and T3 concentration leads to increased serum TSH levels due to negative feedback of the thyroid pituitary axis[4] whereas subclinical hypothyroidism (SCH) shows few or no definitive clinical signs or symptoms. So, it is also sometimes referred to as mild hypothyroidism characterized by an increase in TSH levels whereas serum-free and total T4 and T3 are normal.[5] The patients with SCH are likely to develop OH if left untreated in most of the cases.[6,7] As the condition is mostly asymptomatic, SCH is often diagnosed by a laboratory test.[4] SCH is a far more common disorder than OH. The prevalence of SCH in the general population is estimated at 3 to 8%[8] and the rate of conversion of SCH to OH is around 2 to 5% per year.[7] As stated by various studies SCH has a higher prevalence among women and the older population.[9] The rate of progression of SCH to OH is higher when there is a simultaneous presence of thyroperoxidase antibodies (TPO-Ab) or higher levels of TSH.[10] Prevalence of SCH in Nepal is reported to be 17%,[11] likewise in the Indian population, it is to be around 13.5%.[12]

SCH is a known atherogenic condition and over time it progresses to OH which has a strong association with dyslipidemia which in turn increases overall cardiovascular risk. Several studies have found an association of SCH with lipid abnormalities. The assessment of SCH and lipid abnormalities in such patients can help in the early prevention of the development of OH as well as the prevention of many cardiac abnormalities associated with it.

Hence, in this study, we aim to evaluate the lipid abnormalities in SCH patients with the help of commonly measured laboratory values (TSH, T3, T4, total cholesterol (TC), TG, high-density lipoprotein (HDL), LDL, very low-density lipoprotein (VLDL).

MATERIALS AND METHODS

A hospital-based cross-sectional study was conducted in the laboratory of Nepal Medical College and Teaching Hospital (NMCTH), Attarkhel, Gokarneshwor-8, Kathmandu from August 2021 to April 2022. The study population comprised, a total of 111 cases having SCH (those with SCH: T3, T4 normal, TSH: >4.68 mIU/ml) and 111 cases of healthy (those with normal TFT) controls. Patients aged from 18 years to 75 years were included in our study. Pregnant women and patients on any lipid-lowering drugs as well as patients with diabetes mellitus, renal failure, and any other chronic illness were excluded from this study. For cases, reports of all patients visiting the laboratory for thyroid function tests were evaluated. Those with normal T3 and T4 with TSH above 4.68 IU/ml were considered SCH and were further evaluated for lipid profile until the sample size was reached. History of medication for thyroid dysfunction and any other medical history were taken during blood sample collection. For the control group, a healthy population with normal thyroid function was taken i.e., all the subjects with normal FT3, FT4, and TSH were considered as controls.

Normal values for thyroid profile:

TSH: 0.465-4.68 mIU/ml, fT3: 2.77- 5.27 pg/ml, fT4: 0.78-2.19 ng/dl

In both groups, lipid profiles were assessed. Lipid profile includes TC, TG, HDL, VLDL, and LDL.

Normal values for lipid profile:

TC: <200mg/dl, TG: <150mg/dl, HDL: 30-70mg/dl, LDL: <130mg/dl, VLDL: 15-36mg/dl

Any abnormalities in any of the lipid parameters were considered dyslipidemia.

Thyroid hormone and lipid profile assay: After an overnight fast (8-12 hours), 3 milliliters (ml) of blood samples were collected by venipuncture in all subjects in a gel tube under aseptic conditions and allowed to clot at room temperature. Serum was separated by centrifugation at 3500 rpm for 10 minutes for the separation of serum. Laboratory standard operating procedures were maintained for all laboratory analyses. Serum TSH, fT3, and fT4 were estimated by the Chemiluminescence method by using VITREOUS ECIQ.

All the parameters of lipid profile, TC, TG, and HDL were assayed by dry chemistry method using VITROUS 250 fully automated analyzer from Johnson and Johnson. VLDL and LDL were calculated using Friedewald's formula.

Statistical analysis: Once the sample size was reached, data was edited/ coded and entered into Microsoft excel and were analyzed by using SPSS 16. The normality distribution of the variables was tested. Accordingly, continuous data were expressed as mean (standard deviation) and categorical data as counts (percentages). P values of less than 0.05 were considered as statistically significant at 95% confidence intervals.

As informed verbal consent was taken from all the participants before participating in the study. Their confidentiality and anonymity were maintained. Ethical approval was taken from Nepal Medical College Institutional Review Committee (NMC-IRC).

RESULTS

In our study, the mean age of patients was found to be 50.2 ± 13.3 years and that of control was 45.3±12.5 years and the difference was statistically significant (P=0.005) (Table 1). There were 70.3% (78) female and 29.7% (33) male in the cases group and 58.6% (65) female and 41.4% (46) male in the control group (Fig. 1). The highest number of participants in the cases belonged to age 60-71 years whereas in the control group, it was from 40-49 years (Fig. 2). The subjects in the control group were euthyroid. Elevated TSH level was found in cases Vs controls (6.84 Vs 2.26, P<0.001) which was statistically significant. However, increased fT3 (3.4 Vs 4.04 pmol/L, P<0.001) and fT4 (1 Vs 1.21 pmol/L, P<0.001) were observed among controls compared to cases, which was statistically

Table 1: Age distribution of the participant

Age (Years)	Number	Mean	SD	P-Value
Case	111	50.2	13.3	**0.005**
Control	111	45.3	12.5	
Total	**222**	**47.7**	**13.1**	

P-values <0.05 were considered statistically significant, and are expressed in bold typing.

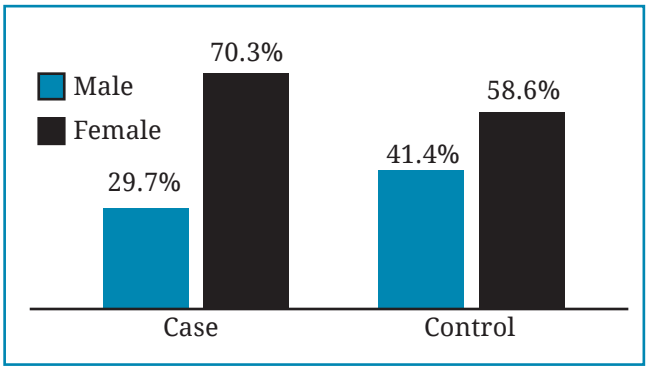

Fig. 1: Gender distribution of the participants among cases and controls

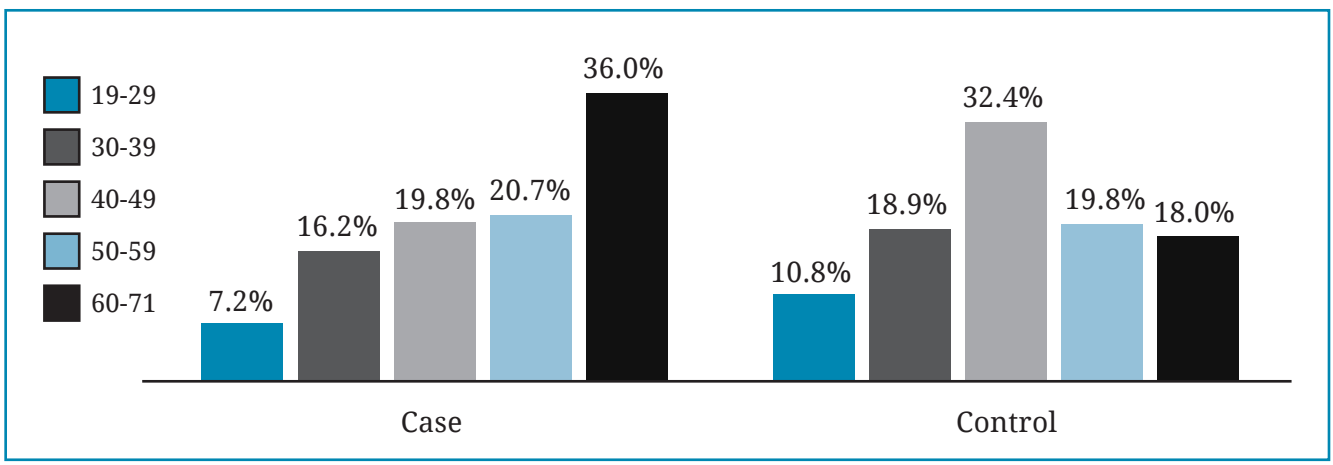

Fig. 2: Age distribution of the participants among case and controls

Table 2: Lipid profile parameters among cases and controls

Variable	Category (mg/dl)	Type						P-Value
		Case		Control		Total		
		Count n	%	Count n	%	Count n	%	
TC	**<200**	86	77.5	92	82.9	178	80.2	0.312
	≥200	25	22.5	19	17.1	44	19.8	
	Total	111	100.0	111	100.0	222	100.0	
TG	**<150**	55	49.5	46	41.4	101	45.5	0.225
	≥150	56	50.5	65	58.6	121	54.5	
	Total	111	100.0	111	100.0	222	100.0	
HDL	**<30**	28	25.2	23	20.7	51	23.0	0.425
	30-70	83	74.8	88	79.3	171	77.0	
	Total	111	100.0	111	100.0	222	100.0	
LDL	**<130**	95	85.6	100	90.1	195	87.8	0.305
	≤130	16	14.4	11	9.9	27	12.2	
	Total	111	100.0	111	100.0	222	100.0	
VLDL	**<15**	2	1.8	5	4.5	7	3.2	0.163
	15-36	73	65.8	60	54.1	133	59.9	
	>36	36	32.4	46	41.4	82	36.9	
	Total	111	100.0	111	100.0	222	100.0	

Abbreviation: TC- Total cholesterol; TG- Triglyceride; HDL- High density lipoprotein; LDL- Low density lipoprotein; VLDL- Very low-density lipoprotein. P-values < 0.05 were considered statistically significant, and are expressed in bold typing.

Table 3: Correlation of TSH with lipid profiles among cases and controls

		Total-cholesterol	TG	HDL	LDL	VLDL
Case	Correlation (r)	-.089	.152	.056	-.118	.152
	P-Value	.351	.110	.560	.216	.110
Control	Correlation (r)	.197	-.009	.196	.132	-.025
	P-Value	.038	.926	.039	.167	.792

P-values < 0.05 were considered statistically significant, and are expressed in bold typing.

significant (Table 4). No significant differences were found between lipid parameters between cases and controls (Table 2) but serum TG, HDL, and VLDL were positively correlated with TSH whereas TC, and LDL was negatively correlated with TSH in the case group though the relation was not statistically significant. Similarly, among control group serum TC, HDL, and LDL were positively correlated with TSH whereas TG, and VLDL were negatively correlated with

Table 4: Baseline characteristics of cases and controls

Parameters	Case Median	Control Median	Total Median	P-value
T3 (pg/ml)	3.4 (2.01-5.22)	4.04 (2.77-5.2)	3.69 (2.01-5.22)	**<0.001**
T4 (ng/dl)	1 (0.66-1.91)	1.21 (0.78-2.15)	1.06 (0.66-2.15)	**<0.001**
TSH (μIU/ml)	6.84 (4.74-40.7)	2.26 (0.5-4.55)	4.65 (0.5-40.7)	**<0.001**
TC (mg/dl)	164 (83-296)	173 (75-281)	165.5 (75-296)	0.362
TG (mg/dl)	151 (68-578)	170 (48-391)	154 (48-578)	0.251
HDL (mg/dl)	39 (15-65)	39 (15-70)	39 (15-70)	0.899
LDL (mg/dl)	90 (26-219.4)	93.8 (16-188)	92.7 (16-219.4)	0.521
VLDL (mg/dl)	30.2 (13.6-115.6)	34.2 (9.6-162)	31.1 (9.6-162)	0.215

Abbreviation: T3- Triiodothyronine; T4- Thyroxine, TSH- Thyroid stimulating hormone; TC- Total cholesterol; TG- Triglyceride; HDL- High density lipoprotein; LDL- Low density lipoprotein; VLDL- Very low-density lipoprotein. P-values < 0.05 were considered statistically significant, and are expressed in bold typing.

no statistical significance. TC and HDL showed a significant positive correlation with TSH in case of controls only (Table 3).

DISCUSSION

Patients with SCH are mostly asymptomatic; hence it may be underdiagnosed. SCH may progress to OH if left untreated and OH is associated with various degrees of thyroid failure and metabolic consequences.[7] Thyroid dysfunction can have important effects on lipid profiles. The correlation between lipid profile and hypothyroidism is well established but lipid profile alteration in SCH is controversial. Different studies have shown different results. Several studies have shown a positive correlation between the thyroid and lipid and if treated on time the changes in lipid can be reversed back to normal, whereas various other studies have shown no correlation between the two.[13-20]

In our study, serum TC, TG, and HDL in cases and controls were not different which is in agreement with the reports by Alamdari *et al.*[21] The results of our study, are contrary to the result of the Colorado thyroid study which showed a modest elevation of TSH accompanied by higher mean TC level than normal TSH.[8] Bayar Qasim *et al*[6] also found an increased level of TC, LDL, and TG in cases than in controls. Concordant to our results, Pirich *et al*[22] revealed no differences in lipid profiles and other cardiovascular risks in the subclinical hypothyroid group in comparison to those with normal TSH levels.

In our study, SCH was more prevalent among female (i.e. 70.3%) compared to male and also it was found that elderly population of 60-71 years age group were more affected than the younger age group which is also the similar findings of Hueston *et al*[20] who stated that by the age of 65 years, the overall prevalence of the disorder is more common in female compared to male. In contrary, Regmi *et al*[13] found the prevalence of hypothyroidism in the age group of 30-50 years. This disparity in the age group could be due to a greater number of elderly patients being referred for the test in our study.

Literatures reporting hypercholesterolemia to be a more common condition in cases with SCH may simply reflect that hypercholesterolemia is a common condition in the general population.[19]

Our observation regarding the association between TSH and lipid levels in the case group found TG, HDL, and VLDL are positively correlated with TSH whereas TC, and LDL are negatively correlated with TSH but with no statistical significance. In a similar study

done by Ferduosi *et al*[17] SCH patients showed a significant positive correlation between TSH and TC, TG. Also, a study done by S. Ashok Kumar found a statistically significant correlation between TSH and TC, LDL, TG, and HDL.[7] Not all studies mentioned reached the same conclusion regarding the presence / lack of association between lipid profiles and TSH levels. NHANES III found no significant association between serum levels of TC, LDL-C, HDL-C, and SCH.[20]

The differences between the results regarding lipid profile of various studies are probably due to different cut-off points used for the definition of SCH, differences in the prevalence of this disorder, and ethnicity, age, and gender of participants.

In this study, association was found between TSH and lipid profiles even in the euthyroid population. TC, HDL, and LDL were positively correlated with TSH and a negative correlation was found between TG, VLDL, and TSH. Similar to these finding, Boekholdt SM in 2010 did a population-based study showing that even in the euthyroid population, there are associations between TSH levels and lipid profiles and they found that TSH was associated with TC, LDL-C, and HDL-C in men and only with HDL-C in euthyroid women.[23]

From these results, we can say that screening for SCH simply to identify lipid abnormalities would be no more useful than screening for hyperlipidemia in general.

Our study showed that SCH may or may not lead to dyslipidemia and even euthyroid group can have lipid abnormalities. So, this concludes that screening for hyperlipidemia in the general population is more useful rather than screening for dyslipidemia in a patient with SCH.

Limitations: This was a hospital-based study, it cannot be applied to the general population. So, large population-based studies are needed to generalize these findings.

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