The Clinical Implications of Thyroid Hormones and its Association with Lipid Profile: A Comparative Study from Western Nepal

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Original Article

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Abstract

Background

Thyroid dysfunction is one of the major public health problems in Nepal. Laboratory tests facilitate early diagnosis before clinical features are obvious, increased sensitivity carries the price of decreased diagnostic specificity. Laboratory tests coupled with supportive clinical findings are frequently used to diagnose thyroid dysfunction. Historically, hypercholesterolemia and raised serum low density lipoprotein (LDL) cholesterol levels have been found to be associated with subclinical hypothyroidism. Therefore, assessment of altered lipid profile plays a supportive role in diagnosis of thyroid dysfunction. The aim of our study was to find out the variations of thyroid hormones and lipid profile in hyperthyroidism and hypothyroidism with their clinical implications.

Materials and Methods

It was a hospital based retrospective study carried out from the data retrieved from the register maintained in the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st July, 2009 and 30th June, 2010. The variables collected were age, gender, T4, T3, TSH, fT4, total cholesterol and triglyceride levels. Descriptive statistics and testing of hypothesis were used for the analysis of data.

Results

122 out of the 365 subjects selected for the study had some form of thyroid disorder. Of the 122 cases, 40 had hyperthyroidism, 42 had hypothyroidism and the remaining 40 were diagnosed to have subclinical hypothyroidism. The frequency of thyroid disorders was much higher in females as compared to their male counterparts. The mean value of each variable in cases, except for age, was statistically significant as compared to controls (p=0.001). Elevated levels of total T3 (CI 2.14 to 2.59), T4 (CI 13.00 to 15.30) and fT4 (CI 2.51 to 2.81) associated with decreased TSH levels (CI 0.29 to 0.35) were found in cases of hyperthyroidism. The TSH values (CI 17.05 to 22.85) were markedly increased while T4 and T3 values were found to be less than the reference range in cases of hypothyroidism. There was significant increase in the mean concentration of total cholesterol (CI 268.83 to 289.79) and triglycerides (CI 154.81to 182.05) in cases of hypothyroidism. The fT4 (CI 1.08 to 1.22) levels were in reference range and TSH levels (CI 9.59 to 10.50) were moderately raised in cases of subclinical hypothyroidism.

Conclusion

Thyroid dysfunction is common across all age groups and shows a strong female preponderance in Pokhara valley. It

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necessitates the measurement of thyroid hormones in women after the age of 50, in pregnancy and after delivery, and in women and men with hypercholesterolemia. Therefore, timely screening and check ups are necessary in order to curtail the problem of undiagnosed cases, giving specific consideration to patients who have high artherogenic profile. This will reduce the risk of future negative health events in older adults.

Key Words
Thyroid hormones, Hyperthyroidism, Hypothyroidism, Lipid profile, Nepal

Background

Thyroid hormones are crucial for growth and for the regulation of protein, carbohydrate and fat metabolism. Thyroid disorders are commonly separated into two major categories, hyperthyroidism and hypothyroidism, depending on whether serum thyroid hormone levels (T4 and T3) are increased or decreased respectively. These disorders may be due to congenital factors, genetic predisposition, inadequate levels of dietary iodine intake, pregnancy, radiotherapy, viral infection, surgery, underlying disease such as infiltrative disorders, or autoimmunity[1-3]. Graves Disease (diffuse toxic goitre) is a common cause of hyperthyroidism due to overactivity of the immune system (autoimmune mechanism). Other causes are sub-acute thyroiditis (painful or viral), silent thyroiditis (painless or postpartum thyroiditis) and toxic multinodular goiter[4]. In the UK, hyperthyroidism has a prevalence of around 2.7% in females, which is approximately 10 times more than the prevalence in males. Thyroid disorders remain undiagnosed in nearly 0.5% of the female population in the UK[5]. In a community survey comprising of 1210 participants (age ≥60 years) from the UK, the prevalence of undiagnosed overt hyperthyroidism was very low[6]. In a similar study conducted in Sweden, out of 1442 participants (age ≥ 60 yrs), only 2% of subjects were diagnosed to have thyrotoxicosis[7]. The leading cause of primary hypothyroidism in iodine deficient areas is Hashimoto's disease (chronic autoimmune thyroiditis)[8]. Pathophysiologically, there is cell-mediated and antibody-mediated destruction of the thyroid gland[9]. Other causes are mainly due to iodine deficiency, over treated Graves disease, anti-thyroid drugs and radioactive therapy. The prevalence of subclinical hypothyroidism ranges from 1% to 10% worldwide and is more common in women than men, with prevalence in women above 60 years of age approaching 20% in some reports[5]. In the United States National Health and Nutrition Examination Survey (NHANES III), the prevalence of overt hypothyroidism and subclinical hypothyroidism was found to be 0.3% and 4.3% respectively[10]. The annual incidence of primary hypothyroidism in women is 3.5 per 1000 and in men 0.6 per 1000 in the UK[11]. Women are 10 times at higher risk of developing hypothyroidism compared to men, with the difference being significant after thirty-four years of age. This is because the symptoms of hypothyroidism and menopause go hand in hand, leaving behind more chances of missing hypothyroid cases[12]. The changing immune environment and the requirements of a growing fetus make pregnancy and the postpartum period complicated, and it can cause thyroid dysfunction[13]. Nepal is a mountainous landlocked area, situated far away from the sea. The geographical placement of the country along with high annual rainfall leads to low soil iodine content. These factors lead to a very high incidence of iodine deficiency disorders. The detection of hyperthyroidism and hypothyroidism in hospital based thyroid screening of suspected patients in eastern part of Nepal was reported to be 13.68% and 17.19% respectively in 2002 and 8.3% in 2010 for each disorder[14].

Both hypothyroidism and hyperthyroidism have potentially fatal systemic manifestations. Therefore, accurate diagnosis of thyroid abnormalities is critical for clinicians as well as medical laboratories worldwide for appropriate management. Laboratory measurements of T3, T4 and TSH are crucial in helping clinicians to diagnose thyroid abnormalities. Historically, hypercholesterolemia and elevated serum low density lipoprotein cholesterol levels have been found to be associated with subclinical hypothyroidism. Therefore, assessment of altered lipid profile plays a supportive role in diagnosis of thyroid dysfunction[15]. The aim of our study was to find out the variations of thyroid hormones and lipid profile in hyperthyroidism, subclinical hypothyroidism and hypothyroidism.

Materials and Methods

It was a hospital based retrospective study carried out using data retrieved from the register maintained in the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st July, 2009 and 30th June, 2010. The variables collected were age, gender, T3, T4, TSH, fT4, total cholesterol and triglycerides.

Analysis of T3, T4, TSH and fT4 levels was done by ELISA (HUMAN)[16-18]. Estimation of total cholesterol and triglycerides was done by CHOD-PAP and GPO-PAP method respectively[19]. All these laboratory parameters were analyzed using Human reagent kits and with the help of ELISA and semi autoanalyser (Humalyser 3500, Germany).

Selection of Subjects:

Inclusion Criteria: Patients with abnormal thyroid profile

Exclusion Criteria: Patients having hepatic or renal dysfunction; history of heart failure, diabetes mellitus, stroke or ischemic heart disease; malignancy; alcohol or drug abuse were excluded from the study. Patients who had used any medications (within the previous six months) that might have contained corticosteroids, antifolates or lipid lowering agents were also excluded from the study.

The data collected was analyzed using Excel 2003, R 2.8.0, Statistical Package for the Social Sciences (SPSS) for

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Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and EPI Info 3.5.1 Windows Version. Z-test was used to compare the significance difference between two variables. A p-value of <0.05 (two-tailed) was used to establish statistical significance.

Results

122 out of the 365 subjects selected for the study had some form of thyroid disorder. Of 122 cases, 40 had hyperthyroidism, 42 had hypothyroidism and the remaining 40 were diagnosed to have subclinical hypothyroidism.

Table 1: Comparison of biochemical variables in cases and controls

Variables	Controls (243)	Thyroid		p value
		Cases	Mean ± SD	
Age	37.95 ± 15.54	Hyper	34.85 ± 16.59	0.248
		Hypo	40.88 ± 15.32	0.258
		Schypo	39.08 ± 17.4	0.678
T3	1.03 ± 0.42	Hyper	2.37 ± 0.74	0.001**
		Hypo	0.37 ± 0.19	0.001**
		Schypo	1.00 ± 0.29	0.571
T4	7.62 ± 1.75	Hyper	14.15 ± 3.7	0.001**
		Hypo	2.21 ± 0.85	0.001**
		Schypo	6.27 ± 1.17	0.001**
TSH	3.0 ± 1.99	Hyper	0.32 ± 0.10	0.001**
		Hypo	20.5 ± 11.4	0.001**
		Schypo	10.04 ± 1.46	0.001**
fT4	1.38 ± 0.36	Hyper	2.66 ± 0.48	0.001**
		Hypo	0.56 ± 0.29	0.001**
		Schypo	1.15 ± 0.21	0.001**
TCHO	167.21 ± 25.90	Hyper	143.12 ± 9.43	0.001**
		Hypo	279.31 ± 34.65	0.001**
		Schypo	257.88 ± 22.29	0.001**
TG	123.53 ± 22.66	Hyper	87.32 ± 18.31	0.001**
		Hypo	168.43 ± 45.02	0.001**
		Schypo	152.35 ± 53.55	0.001**

No. of cases: Hyper - 40, Hypo - 42, Schypo - 40
Hyper (Hyperthyroidism), Hypo (Hypothyroidism), Schypo (Subclinical Hypothyroidism)
T CHO (Total Cholesterol), TG (Triglycerides)
** Statistically significant (p value < 0.05)

Table 1 depicts that mean value of each variable in cases except for age was statistically significant as compared to controls (p=0.001). Elevated levels of total T3 (CI 2.14 to 2.59), T4 (CI 13.00 to 15.30) and fT4 (CI 2.51 to 2.81) associated with decreased TSH levels (CI 0.29 to 0.35) were found in cases of hyperthyroidism. The mean values of total cholesterol (CI 140.20 to 146.04) and triglycerides (CI 81.65 to 92.99) were lowered in cases of hyperthyroidism. The TSH values (CI 17.05 to 22.85) were markedly increased while T4 and T3 values were lowered in cases of hypothyroidism. There was significant increase in the mean concentration of total cholesterol (CI 268.83 to 289.79) and triglycerides (CI 154.81 to 182.05) in cases of hypothyroidism. The fT4 (CI 1.08 to1.22) levels were in reference range and TSH levels (CI 9.59 to 10.50) were moderately raised in cases of subclinical hypothyroidism. The mean values of levels of total cholesterol (CI 250.97 to 264.78) and TG (CI 135.65 to 168.84) was increased as compared to controls in cases of subclinical hypothyroidism.

Table 2: Comparison of gender in cases and controls

Cases	Male	Female	p value
Hyper	10	30	0.001**
Hypo	6	36	0.001**
Schypo	6	34	0.001**
Controls	58	185	0.001**

** Statistically significant (p value<0.05)

Table 2 shows that frequency of thyroid disorders was much higher in females than males in both cases and controls. In suspected cases, percentage of thyroid disorders was 27.5 in males, 35.09 in females and 33.42 overall. It was found to be statistically significant.

Table 3: Gender wise comparison of biochemical variables in cases

Variables	Cases	Male	Female	p value
		Mean ± SD	Mean ± SD	
Age	Hyper	33.00 ± 20.07	35.47 ± 15.61	0.729
	Hypo	53.33 ± 21.80	38.81 ± 13.26	0.168
	Schypo	56.83 ± 25.57	35.94 ± 13.95	0.10
T3	Hyper	2.49 ±.77	2.33 ± 0.74	0.58
	Hypo	0.40 ± 0.10	0.37 ± 0.20	0.66
	Schypo	0.86 ± 0.29	1.02 ± 0.29	0.26
T4	Hyper	14.68 ± 4.76	13.97 ± 3.36	0.67
	Hypo	2.65 ± 0.53	2.13 ± 0.88	0.08
	Schypo	5.86 ± 0.60	6.33 ± 1.24	0.16
TSH	Hyper	0.34 ± 0.11	0.32 ± 0.10	0.62
	Hypo	14.70 ± 5.40	21.48 ± 11.89	0.03**
	Schypo	19.98 ± 9.00	15.34 ± 8.31	0.28
fT4	Hyper	2.5 ± 0.54	2.7 ± 0.47	0.41
	Hypo	0.45 ± 0.25	0.58 ± 0 .30	0.28
	Schypo	1.10 ± 0.60	1.15 ± 0.22	0.25
TCHO	Hyper	145.4 ± 10.12	142.37 ± 9.25	0.42
	Hypo	265.00 ± 23.15	281.69 ± 35.89	0.16
	Schypo	283.50 ± 16.15	265.12 ± 22.25	0.04**
TG	Hyper	84.40 ± 15.98	88.30 ± 19.18	0.53
	Hypo	152.17 ± 42.16	171.14 ± 45.47	0.35
	Schypo	167.50 ± 67.85	176.74 ± 50.59	0.35

No. of cases:Hyper M-10,F-30; Hypo M-6,F-36; Schypo M-6,F-34
** Statistically significant (p value<0.05)

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Table 3 displays that there was quantitatively small gender differences in each variable but they were not statistically significant.

Discussion

Hyperthyroidism is associated with increased mortality in individuals over 60 years of age, particularly from circulatory incompetence and atrial fibrillation[20]. Other effects of hyperthyroidism include decreased systemic vascular resistance, reduced bone mineral density, increased cardiac contractility, cardiac output, heart rate, left ventricular mass causing diastolic dysfunction (delayed relaxation) and atrial arrhythmias. Laboratory tests facilitate early diagnosis before clinical features are obvious, increased sensitivity carries the price of decreased diagnostic specificity. Laboratory tests coupled with supportive clinical findings are used to diagnose thyrotoxicosis and it is best established by showing high circulating concentrations of the thyroid hormones thyroxine (T4) and triiodothyronine (T3)[21]. Thyroid stimulating hormone is undetectable in thyrotoxic patients and may even be normal in some people owing to insensitivity of the assay. The current study showed the rise in serum T3, T4 and fT4 (2.66 ± SD0.48 pg/ml), along with reduced levels of serum TSH (0.32 ± SD 0.10 mU/L). Similar findings were also observed in previous studies in cases of hyperthyroidism[22]. The present study revealed that total cholesterol (143.12 ± SD 9.43 mg/dl) and triglyceride (87.32 ± SD18.31 mg/dl) values were lowered in cases of hyperthyroidism. Thyroid hormones enhance the intravascular catabolism of VLDL triglyceride, modulate LDL receptor activity, both in vitro and in vivo, and hence lowers plasma cholesterol concentrations[23]. Furthermore, there is increased clearance of cholesterol from plasma, excessive conversion of cholesterol to bile acids in the liver and early removal of low density lipoprotein from the plasma in hyperthyroidism[24]. Thyroid hormones also lower triglyceride levels by promoting the clearance from plasma[25].

Hypothyroidism was separated into either overt or subclinical disease. The most sensitive indicator for hypothyroidism was TSH, more than 10 mU/l, along with reduced levels of T4[26]. The present study revealed high values for serum TSH (20.5 ± SD11.4 mU/L) which reflects a reduction in the circulating levels of thyroxine (T4) and triiodothyronine (T3). Hypothyroidism can affect people of all ages. Chronic autoimmune thyroiditis affects women 3-5 times more frequently than men. The mothers with very low serum T4 have higher incidence of still births, abortions and congenital abnormalities, contributing to the higher rate of perinatal deaths as T4 and T3 have strong modulating effect on the immune system. Decreased levels of T4 and T3 due to iodine deficiency during the first trimester could result in abnormal foetal development. Neurological cretinism is characterized by poor cognitive ability, deaf mutism, speech defects and proximal neuromotor rigidity[27]. In our current study, there was significant increase in the mean concentration of total cholesterol (279.31 ± SD34.65mg/dl) and triglycerides (168.43 ± SD45.02mg/dl) in cases of hypothyroidism. A similar study done by Texeira et al in 2008 showed that hypothyroidism could significantly increase the levels of most of lipids, most importantly that of serum total cholesterol and LDL[28]. A study conducted by Risal et al also showed similar mean values of serum total cholesterol (283 ± SD53 mg/dl) in hypothyroid subjects[14]. Hypothyroidism is a cause of secondary hyperlipidaemia. There is usually an increase in total cholesterol and plasma triglycerides levels. The mechanisms responsible for hypercholesterolemia are increased absorption of cholesterol from intestines, decreased clearance of cholesterol and low density lipoproteins from plasma and decreased synthesis of bile acids from cholesterol in the liver in hypothyroidism[24]. There is also significant association between thyroid antibodies, obesity, hypertension, diabetes and hypercholesterolemia. All these factors contribute to elevated risk of coronary heart disease[23]. Lipoprotein Lipase (LPL), a key enzyme in lipid metabolism, catalyzes the hydrolysis of triglycerides (TG) from TG-rich lipoproteins, and serves a bridging function that enhances the cellular uptake of lipoproteins. Triglycerides are elevated due to inactivity of lipoprotein lipase and hepatic lipase, and reduced fractional clearance from plasma in cases of overt hypothyroidism. A study by Wung et al revealed that elevation in plasma TG was less consistent than that of total cholesterol[29]. Therefore, abnormal lipid metabolism in hypothyroidism accelerates the process of atherogenesis and elevates cardiovascular risk[30]. The terminology subclinical hypothyroidism is gaining support, based on evidence that potentially important tissue abnormalities can occur during progressive thyroid failure before the serum T4 concentration becomes clearly subnormal. The increase in TSH levels with free thyroxine (fT4) in reference range defines the grading of subclinical hypothyroidism[31]. In present study, fT4 (1.15 ± SD0.21 pg/ml) levels were in reference range and TSH levels (10.04 ± SD1.46 mU/L) were moderately raised in cases of subclinical hypothyroidism. These values were quite close to values found in other studies i.e. TSH (11.43 ± SD5.50 mU/L) and fT4 (1.05 ± SD0.21 pg/ml)[31]. The current study showed that levels of total cholesterol (257.88 ± SD22.29 mg/dl) and TG (152.35 ± SD53.55 mg/dl) were increased as compared to controls. In similar studies done previously, the levels of serum total cholesterol and TG were found to be 237.50 ± SD1.01mg/dl and 168.53 ± SD 0.89 mg/dl respectively in cases of subclinical hypothyroidism[31]. The major concern with subclinical hypothyroidism has been risk of progression to overt hypothyroidism, hypercholesterolemia and increased risk of cognitive impairment, particularly in elderly individuals[32]. Further, subclinical hypothyroidism may affect both diastolic and systolic cardiac function and worsen traditional risk factors for cardiovascular disease, including blood pressure, plasma lipid profile and endothelial function. Patients with thyroid dysfunction had significant

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reversible alterations in levels of serum total cholesterol and triglycerides.

Conclusion

Thyroid dysfunction is found to be common across all age groups and shows a strong female preponderance in Pokhara valley. Hypothyroidism is reasonably common in people with significant hypercholesterolaemia. It is eminently treatable and this could well result in lipid lowering. It necessitates the measurement of thyroid hormones in women after the age of 50, in pregnancy and after delivery and in women and men with hypercholesterolemia. Therefore, timely screening and check ups are necessary in order to curtail the problem of undiagnosed cases, giving specific consideration to patients who have high artherogenic profile. This will reduce the risk of future negative health events in older adults.

Future Directions of the Study

Multi-centered randomized and population based studies are needed to find the association between hypothyroidism and cardiovascular disorders. Early screening is inexpensive and prevents the progression to hypothyroidism. Antenatal checkups (particularly in the first trimester) help in preventing the premature delivery and birth defects. Maternal iodine supplementation is necessary before or during pregnancy. Iodine deficiency continues to be a major problem in Nepal and demands a clear control strategy, combining ongoing iodine supplementation and education.

Conflict of Interests

The authors do not have any conflict of interest arising from the study.

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