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Research Article

PREVALENCE AND CLINICAL ASPECTS OF THYROID DISORDERS IN HIMACHAL PRADESH, INDIA

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ABSTRACT
The present study determined the prevalence of abnormal thyroid function and their relationship to associated risk factors. Eight hundred twelve patients (Females -750, Males - 62) in the age group of 25-65 (mean age 47±11.54 years) selected from different regions of Himachal Pradesh, India were included in the study. The risk factors associated with thyroid dysfunction viz., smoking, nutritional status, hypertension and obesity were recorded. All the patients were subjected to physical examination and the symptoms related to thyroid dysfunction were noted. The concentration of thyroid stimulating hormone, triiodothyronin and thyroxine was analyzed by enzyme immune assay. Metabolic lesions were found in six hundred fifty six patients (80.7%), non-neoplastic lasions in 111 (13.7%) and neoplastic lesions in forty five (5.54%) thyroid patients. As compared with the non smokers with subclinical hypothyroidism, the smokers with subclinical hypothyroidism had higher serum TSH and T3 concentrations. There was positive association between obesity and serum TSH concentration ($P<0.001$). Serum TSH was higher in the hypertensive subjects, and exhibited linear association with diastolic hypertension. Our results indicate that goiterogenic and antithyroidal substances present in food and water in environment other than iodine deficiency may have role for the persistence of endemic goitre inspite of adequate iodine intake.

Keywords: *Carcinoma, Goitre, Metabolic Lesions, Risk Factors, Thyroid Disorders*

INTRODUCTION
Thyroid hormones are essential in all phases of life cycle, including foetal and neonatal neurological development, overall growth, development, physical and mental efficiency, energy production and reproduction. Diseases of thyroid gland are manifested by alterations in hormone secretion, enlargement of thyroid gland (goiter) or both.

The principal diseases of thyroid gland are goiter (diffuse or nodular), hypothyroidism, hyperthyroidism, thyroiditis and neoplasms. The simple goitre is extremely common throughout the world and is most prevalent in mountainous areas. Thyroid diseases are multifactorial with contributions from genetic and environmental factors (Tsegaye and Ergete, 2003).

Simple goiter is most prevalent in mountainous areas but also occur in non-mountainous areas remote from sea. Iodine deficiency is the major cause for thyroid diseases. Not only the iodine deficiency but increased iodine consumption is strongly implicated as a trigger for thyroiditis. There are a wide variety of chemicals other than iodine that affect the thyroid gland or have ability to promote immune dysfunction in the host (Chandra, 2011). The present study describes the incidence of various types of thyroid disorders after iodine supplementation programme in Kangra Valley, Himachal Pradesh, India.

MATERIALS AND METHODS
Study Design
The present study was conducted on 812 patients in the age group of 25-65 (Mean age 47± 11.54) suffering from various thyroid disorders in Kangra valley, Himachal Pradesh, India. All patients were subjected to thorough history taking and complete clinical examination with special emphasis on manifestations of hypo- or hyperthyroidism and clinical criteria of the goiter and its association with pain. Blood pressure of the patients was measured by using sphygmomanometer.

Exclusion Criteria

Exclusion criteria were the following: postmenopause, pregnancy, severe concomitant diseases, use of drugs that affect metabolism or bioavailability of thyroid hormones preparations, and patients with abnormal urinary iodine

Laboratory Tests

Serum levels of thyroid stimulating hormone, triiodothyronin and thyroxine were estimated by enzyme immune assay tests on ELISA reader.

- Euthyroid (Thyroid hormones within the normal range)
- Subclinical hypothyroid (TSH> 4.5 µIU/ml, T3 and T4 within normal range)
- Overt hypothyroid (TSH> 4.5 µIU/ml, T3 < 0.80 ng/ml and T4 <4.8 µg/dl)
- Subclinical hyperthyroid (TSH<0.45 µIU/ml, T3 and T4 within normal range)
- Overt hyperthyroid (TSH< 0.45 µIU/ml, T3 > 1.90 ng/ml and T4 > 12.0 µg/dl)

Statistical Analysis

Results were presented as Mean ± SD. Measures of significance between groups were calculated using the χ^2 test and analysis of varience (ANOVA) by using SPSS (19.0) statistics package. The symptom index was calculated in the manner of Billewicz *et al.,* (1969). P value less than 0.05 was considered significant.

RESULTS AND DISCUSSION

Results

The pattern of thyroid lesions in studied population is presented in Table 1. Metabolic lesions were found in six hundred fifty six patients (80.7%), non-neoplastic lasions in 111 (13.7%) and neoplastic lesions in forty five (5.54%) thyroid patients. Among patients with metabolic lesions, three hundred sixty six patients (55.7%) suffered from hypothyroidism, while three hundred (45.7%) were affected with hyperthyroidism. In non neoplastic lesions, thyroiditis was most prevalent and was found in eighty nine (80.2%) patients, colloid goitre in sixteen (14.5%) and multinodular goitre in six (5.4%) patients. In neoplastic lesions, papillary carcinoma was most frequent (51.2%) cancer seen in series, followed by follicular carcinoma (26.7%) and medullary carcinoma (22.3%).

Table 1: Pattern of thyroid lesions in the study population

Lesion	Number of Patients	Percentage of Sample
I. Metabolic lesions	(656)	
Hypothyroidism	366	55.79
Hyperthyroidism	290	44.21
II. Non- Neoplastic Lesion	(111)	
Hashmoto's Thyroiditis	45	40.54
Lymphocytic Thyroiditis	24	21.62
Subacute Thyroiditis	20	18.01
Colloid Goitre	16	14.41
Multinodular Goitre	6	5.42
III. Neoplastic Lesions	(45)	
Papillary Carcinoma	23	51.11
Follicular Carcinoma	12	26.67
Medullary Carcinoma	10	22.22

The age distribution of the specific thyroid disease entities are shown in Table 2. Maximum number of patient was in the age group of 45-55 in all type of thyroid disorders. There was a significant trend seen in number of patients from younger to older age group, while last decade showed less number of patients in comparison to 45-55.

Table 2: Distribution of different thyroid lesions in relation with age

Age (Years)	Metabolic lesions	Non- neoplastic lesions	Neoplastic lesions
25-35	134	19	08
35-45	152	26	11
45-55	193	39	17
55-65	177	27	9
Total	656	111	45

The thyroid status of the studied patients is summarized in Table 3. 5.78 % patients were euthyroids, while abnormal thyroid status was observed in 94.22 % patients. There were 56.03% patients with an elevated TSH concentration, most of whom were overt hypothyroid. Among those with an elevated serum TSH concentration, 207 subjects had a level between 4.5 – 10.0 µIU/ml , while 248 subjects had a value greater than 10 µIU/ml. 38.19 % patients were affected with hyperthyroidism. Most of the hyperthyroid patients revealed TSH concentration between 0.10 – 0.39 µIU/ml, whereas only 56 patients had TSH concentration below > 0.10 µIU/ml.

Table 3: Prevalence of thyroid abnormalities in studied population

Thyroid Status	Number of Patients	Percentage of Sample size
Euthyroid	47	5.78
Subclinical Hypothyroid	146	17.98
Overt Hypothyroid	309	38.05
Subclinical Hyperthyroid	110	13.55
Overt Hyperthyroid	200	24.64

Table 4: Frequencies of clinical symptoms in overt and subclinical hypothyroid patients

Symptoms	Overt Hyperthyroidism %age	Subclinical Hyperthyroidism %age	95% Confidence interval	Odd's Ratio
Weight gain	60.11 (220)	25.13 (92)		
Bradykienesis	60.11 (220)	12.29 (45)		
Weakness	59.11 (216)	18.31 (67)	22.48 – 180.36	63.37
Decreased appatite	57.37 (210)	26.78 (98)	4.99 – 21.18	10.28
Constipation	50.54 (185)	20.76 (76)	2.99 – 7.91	4.87
Intolerance to cold	48.91 (168)	17.75 (65)	2.56 – 6.32	4.02
Alopecia	45.91 (168)	8.74 (32)	6.98 – 18.99	11.51
Depression	36.88 (135)	6.83 (25)	4.62 – 12.79	7.69
Coarse skin	28.68 (105)	19.94 (78)	0.53 – 1.21	0.79
Periorbital puffiness	25.68 (94)	9.56 (35)	1.48 – 3.76	2.37
Neck enlargement	19.67 (72)	6.28 (23)	1.54 – 4.41	2.61
Diminished sweating	17.75 (65)	9.56 (35)	0.82 – 2.14	1.33
Cold skin	17.21 (63)	6.28 (23)	1.26 – 3.66	2.15

The frequencies of clinical symptoms among patients of overt and subclinical hypothyroid are shown in Table 4. Overt hypothyroidism patients reported a greater percentage of symptoms than did the

subclinical hypothyroid group. Most frequent symptoms among overt hypothyroidism patients were weight gain (60.11%), bradykienesis (60.11%), weakness (59.11%), decreased appetite (57.37%), constipation (50.54%) and intolrence to cold. However, some symptoms were reported in very low percentage among subclinical group, such as cold skin (6.28%), paresthesias (6.28%) and depression (6.83%). Univariate analysis showed that most of the clinical symptoms differ significantly ($p<0.001$) between overt hypothyroid and subclinical hypothyroid patients, only two symptoms cold skin and diminished sweating showed non- significant difference.

Table 5: Frequencies of clinical symptoms in overt and subclinical hyperthyroid patients

Symptoms	Overt Hyperthyroidism %age	Subclinical Hyperthyroidism %age	95% Confidence interval	Odd's Ratio
Weight loss	58.06(180)	23.87 (74)		
Appetite decreased	58.06 (180)	20.96 (65)		
Fatigue	53.22 (165)	20.32(63)	4.28- 15.71	2.17 – 6.32
Insomnia	47.41 (147)	19.35 (60)		8.21 3.71
Tremor	46.12 (143)	17.41(54)	2.38–6.74	4.01
Heat intolerance	45.16(140)	15.81(49)	2.60–7.29	4.35
Palpitations	43.54(135)	14.51(45)	2.61 – 7.20	4.22
Skin changes	37.09(115)	12.91 (40)	1.89–5.07	3.09
Staring gaze	37.09(115)	11.93 (37)	2.12–5.75	3.49
Exophthalmos Alopecia	36.12 (112)	10.32(32)	2.41–6.69	4.01
Trembling hands	26.77 (83)	9.03 (28)	1.49 – 4.21	2.51
Thyroid enlargement	13.84(54)	5.89 (23)	0.93–2.84	1.62
	9.48 (37)	5.89 (23)	0.55 – 1.76	0.98

The clinical index for the diagnosis of hyperthyroidism is given in Table 5. There was a positive association between proportion of symptoms reported and progressive thyroid failure. Overt hyperthyroidism patients reported a greater percentage of symptoms than did the subclinical hyperthyroid group. Most frequent symptoms among overt hyperthyroidism patients were weight gain (58.06%), appetite decrease (58.06%), fatigue (53.22%), insomnia (47.41%), tremor (46.12%) and intolrence to heat. Univariate analysis showed that all the symptoms differ significantly ($p<0.001$) between overt hyperthyroid and subclinical hyperthyroid patients.

Body mass index (BMI) of an individual is determined by dividing the weight in kilogram by the square of height taken in meters. The mean BMI value in thyroidism patients and euthyroid controls are given in Tables 6 and 7. One way ANOVA with post hoc test described a highly significant ($F = 2084.622$, $P < 0.0001$) variance in BMI value in hypothyroid patients and euthyroids. Tukey – Kramer multiple mean comparison test showed the BMI significantly ($P<0.01$, Table 6) increased in overt hypothyroid patients in comparison to subclinical cases.

Table 6: Body mass index in hypothyroid patients and euthyroid controls

Study group	N	BMI (Kg/m^2) Mean ± SD	q	95% confidence interval
Euthyroid controls	200	23.04 ± 0.59		
Subclinical hypothyroid	146	26.74 ± 1.74*	3.70	3.32 – 4.08
Clinical hypothyroid	220	32.65 ± 1.94*†	9.61	9.27 – 9.95

N - No of hypothyroid patients and euthyroid controls

**P<0.001 vs. euthyroid controls, † P<0.01 vs. subclinical hypothyroid*

One way ANOVA with post hoc test described a highly significant (F = 2084.622, P < 0.0001, Table 9) variance in BMI value within all study groups. Tukey's HSD multiple mean comparison test showed the BMI significantly (P<0.01, Table 7) decreased in overt hyperthyroid patients in comparison to subclinical hyperthyroid patients.

Table 7: Body mass index in hyperthyroid patients and euthyroid controls

Study group	N	BMI (Kg/m^2) Mean ± SD	q	95% confidence interval
Euthyroid controls	200	23.04 ± 0.59		
Subclinical hyperthyroid	110	21.79 ± 1.51	-1.25	-1.50 - -1.00
Clinical hyperthyroid	180	17.82 ± 0.78*†	-5.22	-5.44 - -5.00

N - No of hyperthyroid patients and euthyroid controls.
**P<0.001 vs. euthyroid controls, † P<0.0001 vs. subclinical hyperthyroid*

The mean value of systolic and diastolic blood pressure in hypothyroid patients and euthyroid controls are presented in Table 8 and 9. Systolic and diastolic blood pressure was significantly (P < 0.001) elevated in overt hypothyroid patients compared to euthyroid controls. Subclinical hypothyroid patients also revealed an increase in blood pressure; however the difference was not statistically significant.

Table 8: Systolic blood pressure of hypothyroid patients and euthyroid controls

Study group	N	SBP (mmHg) Mean ± SD	q	95% confidence interval
Euthyroid controls	200	116.53 ± 4.65		
Subclinical hyperthyroid	110	117.32 ± 5.74	0.79	-1.50 - -1.00
Clinical hyperthyroid	180	123.53 ± 6.96*†	7.00	-5.44 - -5.00

N - No of hypothyroid and euthyroid controls.
**P<0.001 vs. euthyroid controls, † P<0.01 vs. subclinical hypothyroid*

One way ANOVA with post hoc test showed a significant (F = 86.211, P < 0.0001) differences in the systolic blood pressure within all study groups. Tukey-Kramer multiple comparison test revealed that increase in systolic blood pressure in overt hypothyroid patients was statistically significant (P<0.01) compared to subclinical cases.

Table 9: Diastolic blood pressure of hypothyroid patients and euthyroid controls

Study group	N	DBP (mmHg) Mean ± SD	q	95% confidence interval
Euthyroid controls	200	82.32 ± 2.31		
Subclinical hyperthyroid	110	85.63 ± 3.24	3.31	-1.50 - -1.00
Clinical hyperthyroid	180	93.65 ± 3.54*†	11.33	-5.44 - -5.00

N - No of hypothyroid and euthyroid controls.
**P<0.001 vs. euthyroid controls, † P<0.01 vs. subclinical hypothyroid*

One way ANOVA with post hoc test showed a significant (F = 749.892, P < 0.0001) differences in the diastolic blood pressure within all study groups. Tukey-Kramer multiple comparison test revealed that increase in blood pressure in overt hypothyroid patients was statistically significant (P<0.01) compared to subclinical cases.

The mean value of systolic and diastolic blood pressure in hyperthyroid patients and euthyroid controls are presented in Table 10 and 11. Systolic blood pressure was significantly (P<0.001) elevated in overt as well as subclinical hyperthyroid patients compared to euthyroid controls. Diastolic blood pressure was also increased in hyperthyroid patients; however the difference was not statistically significant in overt as well as subclinical patients.

Table 10: Systolic blood pressure of hyperthyroid patients and euthyroid controls

Study group	N	SBP (mmHg) Mean ± SD	q	95% confidence interval
Euthyroid controls	200	116.53 ± 4.65		
Subclinical hyperthyroid	110	134.34 ± 9.61*	17.81	-1.50 - -1.00
Clinical hyperthyroid	180	146.35 ± 8.65*†	29.82	-5.44 - -5.00

N - No of hyperthyroid and euthyroid controls.
**P<0.001 vs. euthyroid controls, † P<0.01 vs. subclinical hyperthyroid*

One way ANOVA with post hoc test showed a significant (F = 749.040, P < 0.0001) differences in the systolic blood pressure within all study groups. Tukey-Kramer multiple comparison test revealed that increase in systolic blood pressure in overt hypothyroid patients was statistically significant (P<0.01) compared to subclinical cases. Diastolic blood pressure revealed a non significant elevation compared to subclinical cases.

Table 11: Diastolic blood pressure of hyperthyroid patients and euthyroid controls

Study group	N	DBP (mmHg) Mean ± SD	q	95% confidence interval
Euthyroid controls	200	82.32 ± 2.31		
Subclinical hyperthyroid	110	84.75 ± 2.10	2.43	-1.50 - -1.00
Clinical hyperthyroid	180	86.54 ± 4.32	4.22	-5.44 - -5.00

N - No of hyperthyroid and euthyroid controls.
**P<0.001 vs. euthyroid controls, † P<0.01 vs. subclinical hyperthyroid*

One way ANOVA with post hoc test showed a significant (F = 84.919, P < 0.0001) differences in the systolic blood pressure within all study groups. Tukey-Kramer multiple comparison test revealed that increase in systolic blood pressure in overt hypothyroid patients was statistically significant (P<0.01) compared to subclinical cases. Diastolic blood pressure revealed a non significant elevation compared to subclinical cases.

Discussion

During present study, metabolic lesions were found in six hundred fifty six patients (80.7%), non-neoplastic lasions in 111 (13.7%) and neoplastic lesions in forty five (5.54%) thyroid patients. Among

non- neoplastic lesions thyroiditis (80.2 %) was most prevalent and in neoplastic thyroid disease papillary carcinoma (51.2 %) was most frequent cancer seen in the series. In contrast to our results Tsegaye and Ergete (2003) reported nodular colloid goiter in 76.9 % cases, adenoma in 12.8 %, thyroiditis in 8.2% and carcinoma in 2.1 % cases in a retrospective analysis.

Female (92.37 %) preponderance of the thyroid disease over males (7.63 %) was observed in this study making a female male ratio of 12.1:1. This was in agreement with some previous studies (Mengistu, 1992; Mekones, 1996). A report from Colorado stated a prevalence of elevated TSH (> 5.1 mU/l) of 9.5% in the adult population increasing with age from 3 to 16% in males and from 4 to 21% in females (Canaris *et al.,* 2000). In contrast, Uzunlulu *et al.,* (2007) reported that only female gender was associated with presence of thyroid dysfunction. Ahmad *et al.,* (2009) noted that age, gender, race and area all have an appreciable effect on the levels T4, T3 and TSH.

More symptoms were observed in overt cases in comparison to subclinical and euthyroid subjects in this study. There was a positive association between the proportion of symptoms reported and progressive thyroid failure. Several investigators support the usefulness of multiple symptoms as a diagnostic tool for thyroid dysfunction (Helfand and Crapo, 1990; Canaris *et al.,* 1997; Zulewski *et al.,* 1997). Canaris *et al.,* (2000) reported more symptoms in hypothyroid patients in comparison to euthyroid individuals. Individual symptom sensitivities were low and there was a weak relationship between symptoms reported and thyroid failure.

During present study, morbid obesity (BMI > 35 kg/m^2) was found to be associated with thyroid function disturbances. Thyroid dysfunction was higher in the obese patients as compared to non- obese patients. Knudsen *et al*., (2005) found positive association between BMI and serum TSH ($P < 0.001$) and negative association between BMI and serum free T_4 ($P < 0.001$). Gumieniak *et al.,* (2004) found significantly higher serum TSH levels and significantly lower free T4 index in 194 hypertensive subjects as compared with 90 nonmotensive subjects. When we divide our patients according to systolic and diastolic hypertension, we found high TSH concentration among patients with systolic hypertension.

During present study, both subclinical and overt hypothyroid patients revealed an increase in blood pressure compared to euthyroid controls. Luboshitzky *et al.,* (2002) found that the prevalence of hypertension in the subclinical hypothyroidism group was significantly higher than that in the normal control group, which coincided with our conclusions. Gumieniak *et al.,* (2004) found significantly higher serum TSH levels and significantly lower free T4 index in 194 hypertensive subjects as compared with 90 nonmotensive subjects. Saltiki *et al.,* (2008) showed that subclinical hypothyroidism was an independent risk factor for atherosclerosis and myocardial infarction. Blood hypercoagulability, blood viscosity increment, lipid abnormalities presenting in subclinical hypothyroidism patients could increase the risk for atherosclerosis and these factors may also be involved in pathogenesis in which subclinical hypothyroidism affects the blood pressure.

In this study, the overt hypothyroid patients were found to be more prone to diastolic hypertension. The cause of positive relation between serum TSH and blood pressure is uncertain but several mechanisms have been suggested. Thus it appears to be an increased systemic vascular resistance in subjects with hypothyroidism (Ripoli *et al.*, 2005) and also a positive association between serum- free T4 index and blood pressure salt sensitivity. The increment of systemic vascular resistance may be the main mechanism in overt hypothyroidism patients. T3 can directly act on arterial smooth muscle cells of blood vessels to cause vasodilation (Ojamaa *et al.,* 1996). When hypothyroidism occurs, declining T3 level increases the vascular resistance and the level of blood pressure. Hypothyroidism can also lead to the abnormality of sodium metabolism, the sympathetic nervous system activity raising and the glomerular filtration rate decreasing, which may be involved in the occurrence of hypertension (Gumieniak *et al*., 2004). Blood pressure salt sensitivity was also one of the critical factors for hypertension in hypothyroid patients (Marcisz *et al.*, 2001).

During present study, subclinical as well as overt hyperthyroid patients exhibited systolic hypertension. The diastolic blood pressure did not reveal much variation in hyperthyroid cases. Similarly, Saito and Saruta (1994) found prevalence of hypertension was significantly higher in hyperthyroid patients in the

20-49 years of age. Prisant *et al.*, (2006) documented that prevalence of systolic hypertension is greater among hyperthyroid patients than euthyroids. Hyperthyroidism increases systolic blood pressure by decreasing systemic vascular resistance, increasing heart rate, and rising cardiac output. Conversely, Marcisz *et al.*, (2002) found systolic blood pressure was significantly ($P<0.001$) higher and diastolic blood pressure was significantly ($P<0.01$) in the hyperthyroid cohort than the normal individuals.

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Conflict of Interest
The authors declare that they have no conflicts of interest.

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