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HYPOTHYROIDISM: STUDY OF ENVIRONMENTAL EXPOSURES AS RISK FACTORS

Dr. Poonam Salwan[1], Dr. Megha Sood*[2], Dr. Jagminder K. Bajaj[3], Dr. Shalini Salwan[4], Dr. Sunil Wadhwa[6]

[1]Associate Professor, Department of Pharmacology, SGT Medical College and Hospital, Budhera, Gurgaon.
[2]Associate Professor, Department of Pharmacology, Punjab Institute of Medical Sciences, Garha Road Jalandhar.
[3]Professor and Head, Department of Pharmacology, Punjab Institute of Medical Sciences, Garha Road Jalandhar.
[4]Professor, Department of Pharmacology, Punjab Institute of Medical Sciences, Garha Road Jalandhar.
[5]Senior Consultant, Department of Interventional Cardiology, Rockland Hospital, Dwarka, New Delhi.

***Corresponding Author: Dr. Megha Sood**
Associate Professor, Department of Pharmacology, Punjab Institute of Medical Sciences, Garha Road Jalandhar.

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ABSTRACT

Background: Thyroid diseases are common worldwide. In India too, there is a significant burden of thyroid diseases and 42 million people in India are estimated to be suffering from them. Intentional, inadvertent, or accidental exposures to a variety of environmental factors pose a significant risk of thyroid dysfunction under certain circumstances. There is a need to investigate the potential harm posed by these factors in the quantities commonly encountered. **Objective**: To identify the prevalent risk factors (non-modifiable and modifiable) of hypothyroidism and to estimate strength of their association with occurrence of the disease. **Materials and Methods**: This case–control study was conducted at a teaching hospital in North India. Predesigned and pretested questionnaire was used to collect data. A total of 108 cases with hypothyroidism and 107 control subjects were included in this study. **Result**: About half (54.33%) of hypothyroid patients were in the age group of 40-50 years. Out of total cases, 6.14% were males and 93.8% females. There was significant association between modifiable risk factors (pollution, type of diet and cooking oil) and hypothyroidism, while age and weight as risk factors were not significantly associated. **Conclusion**: Middle aged females seem to be more prone to develop hypothyroidism. Iodine intake ceases to be the sole etiological contender for thyroid disorders. Environmental factors appear to play an etiological role in a significant proportion of patients. The findings provide some insight into the complex interactions between genetic factors, which account for a major part of disease susceptibility, and environmental factors.

KEY WORDS: Thyroid dysfunction, Goitrogens, autoimmune thyroid disease, case-control study, Iodine deficiency.

INTRODUCTION

The problem of hypothyroidism cannot be underestimated in the Indian context. The link between hypothyroidism and iodine deficiency has been extensively researched in India.[1-3] Subsequent to salt iodization program supported by the Government of India, it was shown that in selected regions of Uttar Pradesh, the prevalence of congenital hypothyroidism had come down from 100/1000 to 18/1000.[4] But, autoimmune thyroid disease is probably commoner than iodine deficiency as a cause of goiter in areas that are now iodine sufficient. However, a study showed a significantly higher level of median urinary thiocyanate (USCN) excretion in goitrous subjects (0.75 mg/dl) when compared with controls (0.64 mg/dl; $P < 0.001$). The authors suggested that despite iodization, the prevalence of goiter and hypothyroidism has not dramatically declined.[5]

The researchers noted that thyroid autoimmunity could only partly explain the disease and the role of other goitrogens is an area that needs further study. The environmental factors and endocrine disruptors affecting thyroid hormones and the hypothalamic-pituitary-thyroid axis have not been studied extensively.[6] Circulating concentrations of TSH demonstrate circannual variations. Differences are quite small but the question is whether these variations are an expression of an internal clock or are secondary to environmental effects. The same small circannual changes in TSH are also seen in hypothyroid and T_4-substituted subjects, demonstrating that the changes are independent of the iodine supply.[7]

Of the many minerals known that may affect thyroid function, iodine is the most important. It is an essential substrate for thyroid hormone synthesis and it has been suggested that the increase in dietary iodine content in the United States during the last three decades is

responsible for the higher recurrence rate of thyrotoxicosis.[8] Another important mineral, calcium is said to be goitrogenic when present in diet, in excess. Administration of 2 g calcium per day has been shown to decrease iodide clearance by the thyroid. [9] Another postulation came up that the combined deficiency of iodine and selenium results in myxedematous rather than neurologic cretinism because the decrease in peripheral conversion to T3 results in greater delivery of T4 into the neonatal developing brain.[10] Perhaps the most dramatic study of impact of environmental factors on thyroid is that reported by Kracht, who found that stress provoked thyrotoxicosis in wild rabbits. Although some stress models may prompt secretion of thyroid hormone in animals,[11] this effect is unlikely to occur in humans, at least for a sustained period of time.

Polychlorinated biphenyls (PCBs) have thyroid-disrupting effects as confirmed by animal studies, and it is suggested that phthalates, brominated flame retardants, and perfluorinated chemicals show thyroid-disrupting characteristics.[12, 13] PAHs (Polycyclic aromatic hydrocarbons) are widespread environmental pollutants that are formed in the combustion process of carbonaceous materials.[14] Indoor air is also contaminated by PAHs, which come not only from infiltration of outdoor air but also from indoor emissions such as smoking, cooking, domestic heating.[15–20] Emissions from traffic have been found to be the main outdoor source for the indoor PAH concentration at urban and suburban locations in many industrialized countries.[21] Motor vehicle emissions account for the mass of PAHs in urban areas.[22] There is increasing evidence that environmental exposures, specifically to pesticides, should also be considered potential risk factor for thyroid disease. Animal studies have shown that pesticide exposure to dichlorodiphenyltrichloroethane (DDT), amitrole, and chemicals from the thiocarbamate family can serve as goitrogens[23, 24] and can cause decreased total T4, free T4, total T3, and free T3 levels as well as increased TSH levels.[25] Use of sunscreens has also been associated with hypothyroidism.Benzophenone-2 treated rats exhibited decreased T_4 and increased TSH serum levels.[26]

The discovery of natural and synthetic substances that impair the synthesis of thyroid hormone are landmarks in the history of pharmacology.[27] Dietary goitrogens may have a contributing role in some endemics, and may be the dominant factor in certain areas. These foods including include almond seeds and important dietary items as cassava, sorghum, maize, and millet. Among the plants containing these compounds are cabbage, brussel sprouts, cauliflower, kohlrabi, turnip, rutabaga, mustard, and horseradish, contain cyanogenic glucosides, that upon hydrolysis, release free cyanide.[28] Astwood et al. found that turnips contain progoitrin which undergoes rearrangement to be converted to goitrin, an active goitrogenic thioglycoside.[29, 30] In addition there is a growing list of drugs and diagnostic agents which have been found to affect thyroid economy.

The human exposure scenario with lifelong exposure to a vast mixture of chemicals in low doses and the large physiological variation in thyroid hormone levels between individuals render human studies very difficult. Most of the studies related to thyroid dysfunction are either of the descriptive nature or depict the clinical profiles. As such, analytic type (case–control study or cohort study) has not been carried out in this area of North India; the case–control study of thyroid dysfunction has thus been conducted.

MATERIALS AND METHODS

This case–control study was conducted for one year (i.e., from April, 2017 to March, 2018). The cases and controls were taken from a teaching hospital in North India. Sample size was estimated by using 11% prevalence rate with an allowable error of 15% of prevalence rate. This minimum requisite sample size of patients presenting with thyroid disease was rounded up to the higher side, and, thus, the sample size was achieved by using simple randomization method of sampling. A size of 108 was sufficient to have 99% confidence level and 5% margin of error. Thus, a total of 107 control subjects were obtained from the teaching hospital ensuring that all the other characteristics are comparable except the presence of thyroid disease in the control group. By choosing patients from different set ups belonging to different socio-economic status, we tried to have a blend of heterogeneous subjects, which formed a fairly representative sample whose result can be applied to generalized population.

Inclusion Criteria Cases: All patients of Hypothyroidism >18 years of age (both genders) who were willing to participate in this study. Control subjects: All the subjects >18 years of age (both genders) not having hypothyroidism who were willing to participate in this study.

Exclusion Criteria: Persons who were not willing to participate in the study and had not given written consent and critically ill were excluded from this study.

Data Collection: A predesigned, pretested structural questionnaire was used for data collection. All the questions were explained to the study subjects, and total confidentiality was assured. Ethical clearance for this study was accorded by Institutional ethical committee.

Hypothyroidism risk factor assessment

All recruited subjects underwent personal interview in the form of pre-designed, pre-validated questionnaires that included general features, demographic characteristics, investigations and treatment taken. Specific emphasis was given to identify following 11 risk factors including thyroid disease itself: (1) place of stay, (2) pollution exposure history: We investigated the

role of residential exposure to heavy-traffic roads, as a proxy for traffic-related pollution, (3) smoking, (4) pesticide exposure history: An investigation of pesticide exposure, was prompted by the history of local environmental pollution from the neighboring industrial point sources (5) family history, (6) use of sunscreens (7) age <50 years, (8) Female gender (9) Diet history along with cooking and preference of cooking oil (10) Green tea intake (11) Hypothyroidism.

Statistical analysis

On the basis of pertinent investigations, the persons of both genders >18 years of age were labeled as presenting with hypothyroidism, irrespective of the duration of illness. The data collected was entered into a Microsoft Excel spread sheet and statistical analysis was performed using MS Excel 2007. Inter group comparison of continuous and categorical variables were performed using student's t-test. Correlation of risk factors to hypothyroidism was evaluated by chi-square test. For all tests, alpha was set at <0.05.

RESULT

The age range was 18- 75 years for hypothyroid patients and 19-65 years for the control group. The mean age among the cases was calculated to be 42±14. The differences in mean age of cases and controls were not significant [Table 1]. Similarly, differences in mean weight in cases and controls groups were not significant. A total of 7 (6.2%) cases and 36 (33.6%) control subjects were men while 101 (93.8%) cases and 71 (66.3%) control subjects were women. About 75(69.4%)cases had positive family history of hypothyroidism.[Table 1]. Table 1 shows general information for the study and control group.

Table 1: Sociodemographic and clinical profile of the subjects.

Variables	Cases (n=108)	Control subjects (n=107)	P-Value
Age (Mean ± sd) in years	42 ±14	38±16	p>0.05 (not significant)
Weight (Mean ± sd) in kg	67±17	63 ±16	P>0.05 (not significant)
Gender Female Male	 101 7	 71 36	 26.33 P<0.001(Highly significant)
Family history Yes No	 75 33	 8 99	 19.29 P<0.001(Highly significant)

Table 2 shows the prevalence of environmental risk factors for hypothyroidism among cases and controls. RR for individual risk factor is calculated with *Z* and *P* value for each. It clearly indicates (a) positive and significant correlation with pollution and pesticide exposure history (b) weak and insignificant correlation with place of stay and sunscreen use history.

Table 2: Environmental factors distribution of study subjects.

Variables		Cases (n=108)	Control subjects (n=107)	Chi-square value (p-value)
Pollution Exposure History	Present Absent	95 13	29 77	79.12 P≤0.05 (Significant)
Pesticide Exposure History	Present Absent	101 7	29 6	3.997 P≤0.05 (Significant)
Place of stay	Rural Urban	86 22	92 15	1.912 p>0.05 (Not significant)
Sunscreens use History	Present Absent	27 81	18 85	0.803 p>0.05 (Not significant)

Table 3 shows the cumulative effect of dietary risk factors (four in total) in group based on the total number of these risk factors.

Table 3: Dietary factors distribution in study subjects.

Variables		Cases (n=108)	Control subjects (n=107)	Chi-square value (p-value)
Diet History	Vegetarian Non-Vegetarian	73 35	77 30	11.07 P≤ 0.05(significant)
Preference for raw or cooked food	Raw Cooked	106 2	96 11	5.71 P<0.05(significant)
Cooking oil Preference	Mustard oil Refined oil	30 78	2 105	26.93 P<0.001(Highly significant)
Green tea intake	Never Once a day Twice a day >Twice	90 14 8 1	91 6 0 0	8.8 P≤ 0.05(Significant)

DISCUSSION

By present case-control study, we tried to associate various risk factors for hypothyroidism in a sample of population of this region in North India. Hypothyroidism was found to be a common cause of thyroid dysfunction affecting population. This observation has similarity with a study conducted in other parts of India suggesting a nationwide higher prevalence of hypothyroidism in India.[31-33] There was a predominance of hypothyroidism in women in our study, and is consistent with worldwide report specially those in midlife.[34] In our study, the mean age for hypothyroidism was found to be 42±14, which is quite similar to one of the studies quoting the mean age as 45±14.68.[35] [Table 1]

Benzene-related compounds can lead to thyroid dysfunction,which are very common environmental pollutants which cause damage though polluted air or water. (36) The major sources of these environmental pollutants are tobacco smoke, automobile service stations, exhaust from motor vehicles, and industrial emissions. This study supported our results showing significant association between pollution exposure and thyroid dysfunction.[Table 2]

Another study from 2010 showed an increased risk of hypothyroidism with use of organochlorine insecticides and fungicides.[37] In our study also, cases exposed to pesticides were found to be significantly associated with thyroid dysfunction.[Table2] The negative association observed in our study between pesticides and hypothyroidism is supported by literature.[38] Polychlorinated biphenyls as individual congeners or mixtures in pesticides have repeatedly been shown to alter thyroid function and hormone levels in experimental animals, including thyroid-hormone suppression and cell-mediated immunomodulation.[39-41]

Benzophenone (BP)-type UV filters are found in many sunscreens,lip balms, and other products with SPF. Benzophenones have exhibited disrupting effects towards thyroid hormone receptor, and can also inhibit the activity of thyroid peroxidase (TPO).[42] But we could not find significant association between use of sunscreens and hypothyroidism.[Table 2]

Results reveal that oral administration of green tea extract at 2.5g% and 5.0g% concentrations for 30 days can change the morphology and histology resembling hypertrophy of thyroid follicles as found in hypothyroid due to environment influences associated with significant inhibited activities of thyroid peroxidase(TPO) and 5 monodeiodinase (5 DI1). All these suggest that catechin present in green tea has antithyroidal as well as goitrogenic potential and its regular consumption at relatively high doses pose a threat to the functioning of thyroid.[43] There is some more evidence which shows that the catechins present in green tea might have antithyroid activity when consumed in high doses.[44, 45] But in our study, we could not find any such association.[Table 3] Rather, more cases of hypothyroidism were from the group who had never taken green tea. This discrepancy may be because of the fact that earlier studies involving green tea were carried out on rats, and involved high doses.

Previous reports suggest that a vegetarian diet is associated with reduced risk of hypothyroidism than omnivorous diets in population studies with a follow up of 6 years.[46] On the contrary, in our study, higher number of cases of hypothyroidism was found in the vegetarian group and they were significantly associated.[Table 3] This observation might be because of the fact that several components of the vegetarian diet have been associated with increased risk of thyroid disease including soy products, cruciferous vegetables and low iodine intakes.[47-49]

Raw, boiled and cooked extracts of various cyanogenic plant foods including cauliflower, cabbage, mustard, turnip, raddish, bamboo shoot and cassava have been shown to possess anti thyroid- peroxidase activity. Goitrin is an active goitrogen present in plants of Rutabaga, turnip and Brassicae seeds. However, cooking destroys the enzyme responsible for activation of progoitrin to goitrin thus negating its anti-thyroidal potency.[50] Our study showed positive association

between greater intake of uncooked cyanogenic foods and hypothyroidism.[Table 3]

Although no study has so far been conducted to show the association of edible oils and hypothyroidism, we found a highly significant association between consumption of refined oils and hypothyroidism.[Table 3] However, more studies involving larger population are required to consolidate this fact.

We could not distinguish between prevalent and incident disease, and our exposure measure may not always reflect an exposure that antedated disease onset. Furthermore, we did not have information on timing or level of exposure, and some of the associations were based on small numbers of exposed patients.

In our study group of hypothyroid cases, cooking oil preference for refined oils instead of mustard oil, greater intake of uncooked cyanogenic vegetables, female preponderance, positive family history proved to be highly prevalent out of which first two are modifiable. Place of stay and use of sunscreens, though modifiable prevailed very low. More emphasis should be put on modifying the modifiable risk factors by life-style modifications, drug therapy and other interventions that come well within the domain of family medicine and primary care.

CONCLUSION

Both genetic and environmental factors contribute to susceptibility to hypothyroidism. Middle aged females seem to be more prone. Iodine intake ceases to be the sole etiological contender for thyroid disorders. Marked associations among type of diet, cooking oil preference, pollution and pesticide exposure provide evidence for interactions between genetic and environmental factors; understanding these may allow preventive measures or better tailoring of therapies. Identification of multiple risk factors and plausible underlying mechanisms is warranted. Future epidemiological cohort studies which utilize biomonitoring for specific PAH metabolites or other toxicants in relation to thyroid function may be of some value in determining if such effects exist in humans.

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