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PREVALENCE OF HYPOTHYROIDISM AND ITS CO-MORBIDITIES IN RELATION TO THE CAUSES AND RISK FACTORS IN PATIENTS UNDERGOING LEVOTHYROXINE THERAPY

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ABSTRACT: Hypothyroidism is a metabolic disorder, which results in slower rate of metabolism leading to life threatening medical conditions like diabetes and other complications. This study aims to analyze the prevalence of hypothyroidism and its comorbidities in relation to the causes and risk factors in patients undergoing levothyroxine therapy and to know the adherence level of prescribers to the Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society. **Methods:** This was a cross-sectional, observational, questionnaire-based, single visit study, which included adult patients who were on levothyroxine treatment for at least three months prior to enrolment. Demographic details, data pertaining to etiology of hypothyroidism, the dose of thyroxine used, comorbid conditions, and concomitant medications used were also documented. Compliance to Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society was assessed and documented. **Results** 32% of the study population suffered from primary hypothyroidism. It was also found out that levothyroxine was given along with so many other medication classes with cardiovascular system drugs being the most prescribed medications. Regarding adherence to Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society, only 18 patients out of 59 patients who have elevated lipid levels were subjected to tests for hypothyroidism. **Conclusion:** This study warrants the inclusion of thyroid profiling as a compulsory evaluation parameter in all patients who are obese and in those who report elevated lipid profiles. Higher prevalence in female population in this study calls for larger studies focused on the female population. Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society should be brought to practice if we are interested in preventive care.

INTRODUCTION: Thyroid hormones, Triiodothyronine (T3) and Thyroxine (T4), individually or combined, when elevated or reduced, have an effect on blood glucose homeostasis¹. Increased levels of free circulating thyroid hormones (hyperthyroidism) leads to hyperglycemia due to polyphagia, increasing glucose absorption from the gastrointestinal tract, accelerating insulin degradation and stimulating glycogenolysis².

Reduced levels of the hormones (hypothyroidism) may cause hypoglycaemia^{2, 3}. The occurrence of thyroid dysfunction is higher in diabetes patients. This is estimated to be 10 to 15% in diabetes compared to 6% in the non-diabetic population^{4, 5, 6}. Many studies reported and justified this finding in type 1 diabetes patients^{4, 5, 7, 8} and fewer studies reported the same findings even in type 2 diabetes^{9, 10}. Hypothyroidism is a common disorder where the amount of hormone secreted by the thyroid gland is inadequate to meet the body's needs.

The main function of thyroid hormone is to stimulate metabolism. Hence, hypothyroidism results in slower rate of metabolism. The symptoms of hypothyroidism can vary considerably from person-to-person. If not diagnosed and treated,

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hypothyroidism can, in some cases, become severely debilitating or fatal. Most physicians recommend thyroid-replacement therapy for patients with grossly elevated TSH levels (suggesting more pronounced hypothyroidism); whereas, the risk/benefit ratio in treating patients with only slightly increased TSH values has been a topic of considerable debate. Medical texts and review articles are almost unanimous in recommending levothyroxine (T4) as the only appropriate treatment for hypothyroidism. Appropriate hormone-replacement therapy will ameliorate the clinical manifestations of the disease, allowing most affected individuals to have a close-to-normal quality of life.

T4 is the mostly acceptable thyroid replacement option. The reason for recommending only T4 is that peripheral (i.e., extrathyroidal) tissues are capable of converting T4, which is prohormone, into its biologically active form, T3. Thus, administration of T4 provides a constant reservoir from which the body can meet its needs for T3^{11, 12}. Most authorities discourage the use of T3-containing preparations for thyroid replacement therapy because T3 is rapidly absorbed and has a relatively short half-life, resulting in wide between-dose fluctuations in serum T3 levels that are not physiologic.

Many disorders may respond to thyroid hormone like depression, reactive hypoglycemia, ENT disorders, menstrual disorders, infertility, premenstrual dysphoric syndrome, fibrocystic breast disease, polycystic ovary syndrome, certain dermatological conditions, asthma, hypertension, and certain cardiovascular diseases¹³.

Thus, thyroid hormone replacement may indirectly treat or target many diseases. About one-fourth of the patients with subclinical hypothyroidism have a total cholesterol concentration higher than 6.2 mmol/L. A cross-sectional, population-based study from the Netherlands found that the prevalence of subclinical hypothyroidism was correlated with lipid levels; the prevalence was 4% among women with a total cholesterol level < 5 mmol/L; 8.5% when total cholesterol was 5 to 8 mmol/L; and 10.3% when total cholesterol was > 8 mmol/L¹⁴. Another recent cross-sectional study of 279 women

over the age of 65 found a strong relationship between hyperlipidemia and serum TSH levels¹⁵. Men with a mildly elevated TSH generally do not have an increased risk for hyperlipidemia, but data on men are sparse. Hypercholesterolemic men do not have a higher prevalence of subclinical hypothyroidism than men with low lipid levels¹⁴. Subclinical hypothyroidism is relatively common among hypercholesterolemic patients.

Thus, the measurement of serum TSH levels should be included in the screening of patients with dyslipidemia^{16, 17, 18}. As per the Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society, overt hypothyroidism is associated with the risk of cardio vascular disease because it increases LDL cholesterol and hypertension. It advises that doctors screen patients with dyslipidemia for abnormal thyroid levels and accordingly prescribe treatment. Hence, the principal aim of this study is to analyze the prevalence of hypothyroidism and its comorbidities in relation to the causes and risk factors in patients undergoing levothyroxine therapy and the adherence level of our prescribers to the Thyroid Dysfunction and Dyslipidemia Guidelines guidelines of Indian Thyroid Society.

MATERIALS AND METHODS:

Study design:

This was a cross-sectional, observational, questionnaire-based, single visit study, which included adult patients who were on levothyroxine treatment for at least three months prior to enrolment. The study was conducted between May 2014 and February 2015, spanning for a 10-month period. The study was conducted in a southern district of Tamil Nadu, India. Five leading endocrinologists were selected and patients from these five endocrinologists were enrolled in the study. The study was conducted in accordance with the International Conference on Harmonization (ICH-GCP) and regulations and guidelines having their origin in the Declaration of Helsinki. Written informed consent was obtained from all the participants prior to the study.

Participants:

Patients aged between 12 and 60 years diagnosed with primary or secondary hypothyroidism were

enrolled in the study. They were required to be on treatment on any available brand of levothyroxine for at least three months before enrollment in to the study. The patients who are on tri-iodothyronine (T3) therapy, pregnant women, lactating women, those with decreased mental capacity, and those with central hypothyroidism and transient hypothyroidism were excluded from the study.

Measurements:

Demographic details, medical history, laboratory values, vital signs, and physical examination were recorded for each participant. Data pertaining to etiology of hypothyroidism, the dose, duration, and brand of thyroxine used; comorbid conditions, and concomitant medications used were also documented. Compliance to Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society was assessed.

RESULTS: A total of 341 patients were enrolled in the study across five leading endocrinology hospitals in Southern Tamil Nadu, India and all the subjects completed the study. Out of 341 patients, 160 of them were males (46.9%) and 212 of them were females (62.2%) with a mean age of 54.44. In age wise distribution, the highest number of patients (29%) fell in 45 to 55 years of age range followed by 23% in 35 to 45 years range. According to the educational status, the highest number of patients who were diagnosed with hypothyroidism were found to be in the higher secondary category (36.4) followed by below SSLC category (22.3%). 49% of patients were in the overweight range followed by the 18.5% in the obese range followed by the normal BMI range 16.1% followed by 15.8% in the beyond obese range. This can be shown in **Table 1**.

TABLE 1: SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE PARTICIPANTS

Variables	Frequency (N = 341)	Percentage (%)
Sex		
Male	160	46.9
Female	212	62.2
Age		
<5 years	0	0.0
5.1-15 years	20	6.0
15.1-25 years	18	5.2
25.1-35 years	46	13.5
35.1-45 years	78	23.0
45.1-55 years	99	29.0
55.1-65 years	74	21.6
65.1-75 years	6	1.7
>75 years	0	0.0
Education		
<SSLC	76	22.3
SSLC	33	9.7
HSC	124	36.4
Diploma	13	3.8
UG	49	14.4
PG	34	10.0
Not Available/ Nil	12	3.5
BMI		
<18	3	0.9
18.1-24	55	16.1
24.1-29	167	49.0
29.1-35	63	18.5
>35.1	54	15.8
Social Habits		
Products of Tobacco	45	13.2
Smoking	53	15.5
Alcohol	47	13.8
Betel/ Lime & Tobacco/Hans	32	9.4

From the data obtained from the social history, it is clear that 15.5% were smokers and the next highest social habit was alcohol use to the tune of about 13.8% (47). The patients using tobacco in the raw

form or in the scented form amounts to 45 and 32 patients (9.4%) used snuff or Hans or the betel leaves and nuts regularly. This can also be shown in **Table 1** above.

Data obtained from past medical history shows that 149 (43.7%) of the patients out of the 341 study group suffered by obesity 96 (28.2%) suffered with diabetes followed by 84 (24.6%) with menstrual disturbances, 77 (22.6%) hypertension, followed by 63 (18.5%) with respiratory disorders like Asthma or COPD and finally 7 (2.1%) had undergone surgery in the past. In terms of co-morbidities, weight gain was the primary co-morbidity that the patients contracted after the diagnosis of hypothyroidism with amount totaling to 48.1% of the total study population. The next major ailment

contracted was lethargy with 30.8% of people experiencing it followed by menstrual disturbances in 27% of people followed by hyperlipidemia in 20.8% followed by anemia, dry hair, tachycardia, and other dermatological problems like dry skin and dermatitis in 16.4%, 13.2%, 12.6%, and 10.9% respectively followed by cold intolerance, PCOD and other related problems in less than 10% of the entire study population. This can be seen in **Table 2**.

TABLE 2: DISTRIBUTION OF PARTICIPANTS ACCORDING TO THE MEDICAL HISTORY AND COMORBIDITIES DIAGNOSED WITH OR AFTER DIAGNOSIS OF HYPOTHYROIDISM

Variables (%)	Frequency (N = 341)	Percentage (%)
Medical History		
Obesity	149	43.7
Diabetes	96	28.2
Menstrual disturbances	84	24.6
Hypertension	77	22.6
Asthma/COPD	63	18.5
Surgery	7	2.1
Comorbidity With/After Hypothyroidism		
Weight gain	164	48.1
Lethargy	105	30.8
Menstrual irregularities	92	27.0
Hyperlipidemia	71	20.8
Anemia	56	16.4
Dry hair	45	13.2
Tachycardia	43	12.6
Psoriasis/Urticaria	37	10.9
Cold intolerance	24	7.0
PCOD	19	5.6
Constipation	11	3.2
Seizure	11	3.2
Goitre	9	2.6

Out of the 341 study population, 109 (32%) were suffering from primary hypothyroidism followed by 84 (24.6%) suffering from overt hypothyroidism followed by 73 (21.4%) suffering from subclinical hypothyroidism followed by 57 (16.7%) with secondary hypothyroidism followed by 18 (5.3%) suffering from acquired hypothyroidism. From the data obtained from the dose of levothyroxine used,

it is evident that people who consumed between 50-75 mcg of levothyroxine were the highest amounting to 153 (44.9%) followed by 87 (25.5%) consuming 25-50 mcg followed by 58 (17%) consuming less than 25 mcg followed by 26 (7.5%) consuming 75-100 mcg of levothyroxine. This can be seen in **Table 3**.

TABLE 3: TYPES OF HYPOTHYROIDISM AND DOSES OF LEVOTHYROXINE USED AND CO-PRESCRIBED DRUGS

Variables	Frequency (N = 341)	Percentage (%)
Types of hypothyroidism		
Primary	109	32.0
Secondary	57	16.7
Acquired	18	5.3
Overt	84	24.6
Subclinical	73	21.4

Levothyroxine Dose		
<25 mcg	58	17.0
25-50 mcg	87	25.5
50-75 mcg	153	44.9
75-100 mcg	26	7.6
>100 mcg	17	5.0
Co-prescribed Medications		
Cardiovascular Drugs	161	47.2
Anti-diabetic Drugs	114	33.4
Hormonal Drugs	97	28.4
Respiratory Drugs	79	23.2
Gen. health enhancers/Nutritional supplements	73	21.4
Circulatory System Drugs		
Neurology Drugs	64	18.8
	18	5.3

Number of prescriptions containing drugs co-prescribed along with levothyroxine was 161 (47.2%) of CVS drugs, followed by antidiabetic drugs 114 (33.4%), hormonal drugs 97 (28.4%), respiratory drugs 79 (23.2%), nutritional and multivitamin supplements amounting up 73 (21.4%), circulatory drugs 64 (18.8%), and 18 (5.3%) neurological drugs, which can also be seen in the above **Table 3**.

Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society recommends all patients with elevated lipid levels be screened for hypothyroidism. In the entire patient group, 59 patients had elevated lipid levels in the past and they were aware of their elevated lipid levels, but when it comes to the adhering to the guideline, the following data was obtained - only 18 members (5.3%) of the overall population with elevated lipid levels were subjected to the tests of hypothyroidism and the rest 41 (12%) of the total population were not subjected to hypothyroidism tests in line with the Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society. This is shown in **Table 4**.

TABLE 4: ADHERENCE TO THYROID DYSFUNCTION AND DYSLIPIDEMIA GUIDELINES OF INDIAN THYROID SOCIETY

Adherence Status	Frequency (N = 341)	Percentage (%)
Adherent	18	5.3
Non-adherent	41	12.0

Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society - Recommends all patients with elevated lipid levels should be screened for hypothyroidism

Hypothyroidism is a know outcome of the use of lithium or amiodarone in the past. From the data obtained, it is evident that 4 out of 341 patients (1.2%) had used amiodarone in the past and 3 out of 341 patients (0.9%) had used lithium shown in **Table 5**.

TABLE 5: USE OF AMIODARONE AND LITHIUM AS A CAUSE OF HYPOTHYROIDISM

Amiodarone/Lithium	Frequency (N = 341)	Percentage (%)
Amiodarone	4	1.2
Lithium	3	0.9

Accidental diagnoses made when laboratory tests were prescribed to understand the type of hypothyroidism were shown in **Table 5**. The first was hyperlipidemia which was found in 34 (10%) of the patients followed by anemia 16 (4.7%), hypoglycemia 12 (3.5%), osteoporosis 9 (2.6%), hypertension 5 (1.5%), and finally electrolyte imbalance in 2 (0.6%) patients. This can be seen in **Table 6**.

TABLE 6: CO-DIAGNOSED CONDITIONS WITH HYPOTHYROIDISM

Conditions	Frequency (N = 341)	Percentage (%)
Hyperlipidemia	34	10.0
Anemia	16	4.7
Hypoglycemia	12	3.5
Osteoporosis	9	2.6
Hypertension	5	1.5
Electrolyte imbalance	2	0.6

DISCUSSION: BMI data obtained from this study proves and is in line with various data and various studies across the globe that BMI is directly

correlated with a wide variety of diseases like the diabetes, hypothyroidism, dyslipidemia, and coronary artery diseases. Amongst the social habits, 15.5% were smokers and the next highest social habit was alcohol use to the tune of about 13.8%. These also have a correlation with both the national and international studies. There were two basic objectives of this study, one was to find out what was the past history and what are the co-morbidities, meaning whether there was any correlation between any past history in acquiring this disease or whether this disease had led to any other disease or co-morbidity and it proved that most of the patients had past medical history of some diseases and almost all patients had some level of co-morbidity developed because of hypothyroidism.

In our study, it was also evident that 32% of the study population suffered from primary hypothyroidism, which is the most prevalent type of hypothyroidism. It is evident from all the Indian and international literatures that hypothyroidism co-exists with many other disorders which needs to be taken care of. In this study also, it is found out that levothyroxine is given with so many other classes of medications with CVS drugs being the most prescribed medications. Regarding adherence to Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society, 59 patients had elevated lipid levels in the past and they were aware of their elevated lipid levels out of which only 18 were subjected to tests of hypothyroidism, which is a clear indication that Indian Thyroid Guideline is still in books and not in practice. Hypothyroidism is a known outcome of the use of lithium or amiodarone in the past.

Out of 341 patients, many could not understand or answer our question on this topic, though some could remember and answer. 4 out of 341 patients had used amiodarone in the past and 3 out of 341 patients had used lithium. The data may not be so relevant as the medical records are not available to substantiate the claim. Like the accidental discoveries, there are accidental diagnoses with the main disease when the laboratory tests are prescribed to understand the other conditions to treat the cause and understand the type of hypothyroidism and in this study, there were many

co-diagnosed conditions along with hypothyroidism, which was only known when hypothyroidism was diagnosed, not before or after).

CONCLUSION: More hypothyroidism cases were reported in the female population and in the age group 45.1-55 years, the post menopausal age range. As high as 49% of the study population fell under the overweight BMI group, that may also explain the prescription of more amounts of cardiovascular and antidiabetic drugs for the co-morbidities. One leads to other and the chain continues till the vicious cycle is broken by an efficient mechanism, and early intervention is the key to preventive medicine. 48.1% study population reporting obesity after experiencing/diagnosing hypothyroidism explains the complementary link between the elevated lipid profiles versus obesity versus hypothyroidism. This study gives some insight in this area in relation to the non-adherence of the Thyroid Dysfunction and Dyslipidemia Guidelines of Indian Thyroid Society in practice and how important it is to adhere to the above said guideline. The most famous quote 'prevention is better than cure' is still on books. There is no dearth for guidelines in India, but ignorance or non-adherence to the same are like having a helmet and not wearing it.

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