ISSN 2515-8260 Volume 09, Issue 01, 2022

Cardiovascular Involvement in Hypothyroidism – A Case Study

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Abstract
Both subclinical and clinical forms of thyroid disease—hypothyroidism and hyperthyroidism—have become more frequent in recent years. The NHANES III Study followed people aged 12 and above over the course of 6 years, and found that the prevalence of hypothyroidism was 4.6% (0.3% clinical and 4.3% subclinical) while the prevalence of hyperthyroidism was 1.3% (0.5% clinical and 0.7% preclinical).

Introduction

When it comes to the clinical manifestations of thyroid illness, cardiovascular consequences consistently rank among the most severe and reliable. Heart disease deaths and hospitalisations are both higher in those with hypothyroidism. Disfunction may be mild, such as systolic or diastolic dysfunction, or severe, such as in overt failure or coronary artery disease.

Clinically seen as a broad slowdown of metabolic processes, hypothyroidism is a condition caused by a lack of thyroid hormones. The prevalence of hypothyroidism is high, affecting 2-4% of adult females and 0.02%-0.04% of adult males. Almost every tissue in the body responds to thyroid hormones via direct cellular actions. The metabolic disruption it creates manifests itself in several organs.

The purpose of this research is to better understand the cardiac symptoms of hypothyroidism in order to reevaluate the importance of early detection and more active care of the condition to avoid the aforementioned problems.

Objectives

1. "To study cardiovascular manifestations in newly diagnosed hypothyroid patients by electrocardiogram and two-dimensionaltransthoracic echocardiogram and chest radiograph."
2. "Early diagnosis and treatment of cardiac diseases in hypothyroidpatients"

Anatomy and Development:

Since the thyroid is so conveniently situated, it may be easily examined and felt. Two lobes of the thyroid gland are joined by an isthmus in a healthy adult thyroid gland. The colour of thyroid tissue is a pale brown, and its sliced surface often has a reflective sheen. The average gland weighs between 15 and 25 g and is encased in a thin, fibrous capsule. In a healthy individual, the ties that bind the thyroid to its surrounding tissues are relatively weak, and the thyroid itself sits on its own, separate fascial planes. Each lobe of the thyroid contains four parathyroid glands, the source of the hormone parathyroid. In order to prevent paralysis of the

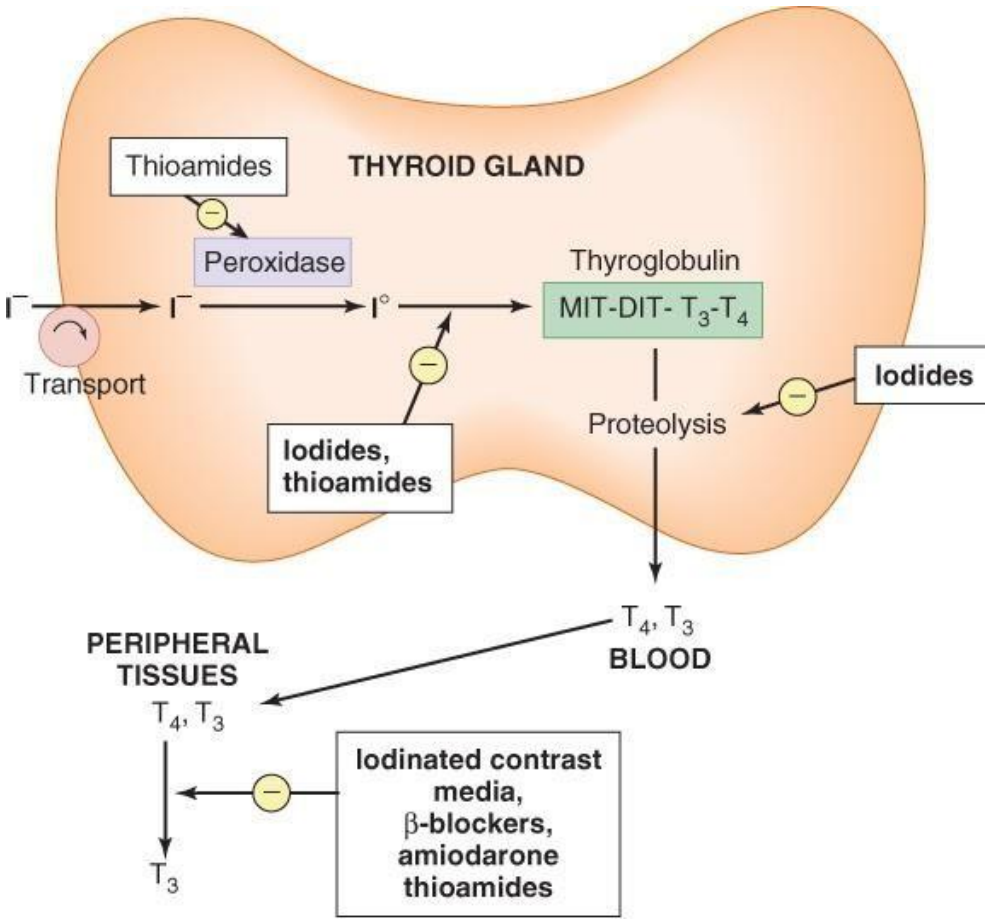
ISSN 2515-8260 Volume 09, Issue 01, 2022

vocal cords during thyroid surgery, it is essential to locate the recurrent laryngeal nerves, which run along the lateral margins of the thyroid gland.

TSH regulates the primary synthetic stages including iodide transport, organification, coupling, thyroglobulin (Tg) production, and endocytotic secretion. Thyroid cells respond to TSH by removing iodide from their basal capillary network and transporting it to their apical cytoplasm, where it is combined with molecules of tyrosine to produce mostly T4 and a little amount of T3. Colloid is where the thyroid gland stores its T4 and T3 in the follicles. After that, they are both released at once, or at least part of the T4 gets deiodinated to T3 before being let go. TSH and other proteins that bind to the TSH receptor may also affect these two processes.

"Mutations of this TSH receptor are continuously activated in some toxic adenomas and multinodular goiter".[10] "A small but measurable amount of non-TSH-dependent T4 secretion also occurs normally".[11] Tg is a 660 kDa glycoprotein that contains the tyrosine residues involved in the iodine organification reaction. Some occurrences of goitre have been linked to defects in Tg synthesis, albeit this is a very unlikely explanation. Tg serum levels are a helpful marker of biologic activity or recurrence in the therapy of well-differentiated thyroid carcinoma.[12]

Figure 2: Synthesis and transport of thyroid hormones



Thyroid hormone action:

Thyroid hormones act by binding to nuclear receptors, called thyroid hormone receptors (TRs) α and β. "Both TRα and TRβ are expressed in most tissues, but their relative levels of expression vary among organs; TRα is particularlyabundant in brain, kidney, gonads, muscle, and heart, whereas TRβ expressionis relatively high in the pituitary and liver. Both receptors are variably spliced toform unique isoforms. The TRβ2 isoform, which has a unique amino terminus, is selectively expressed in the hypothalamus and pituitary, where it appears toplay a role in feedback control of the thyroid axis. The TRα2 isoform contains a unique carboxy terminus that prevents thyroid hormone binding; it may functionto block the action of other TR isoforms."

TRs have a DNA-binding domain in the middle and a ligand-binding domain at the end. They interact with thyroid response elements (TREs), which are found in the gene promoters of their intended targets (Figure 2). Depending on the characteristics of the regulatory elements in the target gene, an active receptor may either increase gene transcription (as in the case of the myosin heavy chain α gene) or inhibit transcription (as in the case of the TSH -βsubunit gene).

Hypothyroidism:

Hypothyroidism, caused by a lack of thyroid hormone, is a common endocrine condition. It's the main reason why the thyroid gland produces too little of the hormone thyroxine. Failure of sufficient pituitary thyrotropin (TSH) or hypothalamic thyrotropin-releasing hormone (TRH) production may also cause hypothyroidism, which is referred to as secondary hypothyroidism (secondary or tertiary hypothyroidism). Patients may show up with no symptoms to, very infrequently, a coma and multi-organ failure (myxedema coma). The purpose of the Whickham survey was to collect data on the prevalence of thyroid illness in the community at large.[16]

More than 2% of 2800 people tested positive for hypothyroidism after being diagnosed based on their medical history and bloodwork. The average patient was 57 years old at diagnosis, and females were affected by the condition 10 times more often than males. Most cases occur in women over the age of 40. Hypothyroidism is common in frail elderly people of both sexes.[17]

Epidemiology

The incidence of overt hypothyroidism was found to be 0.3% in the NHANESIII (National Health and Nutrition Examination Survey) research, whereas the prevalence of subclinical hypothyroidism was found to be 4.3% in the same population. Thyroid stimulating hormone (TSH) and the presence of antithyroid antibodies were shown to increase with both female gender and chronological age.[22]

Pathophysiology

Thyrotropin-releasing hormone (TRH) is released from the brain and stimulates the pituitary gland to release thyroid-stimulating hormone (TSH). To a greater extent than T3, T4 is generated and secreted in response to thyroid stimulating hormone, whereas T3 is primarily synthesised from T4. In turn, the T3 and T4 levels have a negative feedback effect on the

generation of TRH and TSH. Hypothyroidism may develop as a consequence of changes in the structure and function of any of these organs or pathways.

Antithyroid antibodies rise after birth, leading to postpartum thyroiditis, which manifests during the first year following delivery and affects 5-10% of women. In some cases, it manifests as moderate hyperthyroidism that gradually converts to hypothyroidism and resolves without treatment, whereas in others, it manifests solely as hypothyroidism and requires treatment with thyroxine for up to six months. However, hypothyroidism might linger for four years or more in 25% of patients.

When you have silent thyroiditis, you could notice that your hyperthyroidism is rather modest and has only just started. Thyroid hormones are released into the bloodstream as a result of cellular death; this condition lasts for 6-12 weeks and often resolves on its own, however in 50% of instances it progresses to transitory hypothyroidism, which lasts for 2-12 weeks. Hypothyroidism is a condition that, in only around 5% of instances, may be permanent.

Memory loss, agitation, irritability, and other cognitive difficulties, including sadness and anxiety, are all possible manifestations. Ascites, rhabdomyolysis, and pericardial effusion are all very unusual symptoms that patients may have. Patients may also exhibit symptoms of congestive heart failure, extended QT interval, hypercholesterolemia, hyponatremia, and carpal tunnel syndrome. Thyroid enlargement, nodules, a slow relaxation of the ankle reflex, hoarseness, skin and hair changes, periorbital edoema, and pallor may be detected during a physical exam.

Thyroid dysfunction syndromes (hyper and hypothyroidism) are known to affect the cardiovascular system in number of ways.[48] While hyperthyroidism's immediate effects on the heart and blood vessels are evident, evidence for the chronic consequences of thyroid disease on the heart and on cardiovascular outcomes is less conclusive.

This is true much more so for hypo and hyperthyroidism in their more subtle or preclinical stages. No correlation was discovered between early hypothyroidism, elevated serum TSH levels, or antithyroid antibodies with the onset of coronary artery disease, for example, in a 20-year follow-up analysis of the original Whickham Survey. Aortic atherosclerosis and myocardial infarctions were shown to be substantially more common in individuals with subclinical hypothyroidism, according to the more recent Rotterdam study49. Thyroid autoimmunity was not linked to an increased risk of cardiovascular disease in either the Whickham Survey or the Rotterdam research.

Material and Methods

Cross sectional descriptive study

Source of Data: Patients, both male and female with hypothyroidism presenting to the OPD and patients admitted in KRISHNAHospital were included in this study.

Sample size: Convenient sampling technique was used in the presentstudy to enroll the 100 study subjects fulfilling inclusion criteria in the study duration.

Study duration: December 2017 to May 2019 for a period of 18 months

Sampling technique: Simple Random Sampling.

Inclusion criteria for case selection:

A. All the diagnosed cases of hypothyroidism coming to out-patient department of Medicine during study duration.

B. All the diagnosed cases of hypothyroidism admitted under department of Medicine during the study duration.

C. Cases giving informed written consent.

D. More than 18 years and less than 80 years of age.

Exclusion criteria for case selection:

A. "Patients with known cardiac disease"

B. "Patients with chronic obstructive pulmonary disease, severe anemia, diabetes mellitus or any other endocrinal disorder."

C. "Patients taking medications that alter the thyroid function like beta blockers, lithium, oral contraceptive pills, steroids & alcohol."

Methods:

- Patients with hypothyroidism presenting to the department of Medicine, outpatient department or indoor wards in Krishna Institute of Medical sciences and Hospital were studied over a period of 18 months.

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- The demographic characteristics of the cases were noted, clinical, medical, family history, social history was also recorded with the help of standard, semi-structured, pre-validated case record proforma.

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- Patients were subjected to various investigations as follows:

Investigations:

- **T3, T4, TSH:** 3 ml of early morning fasting samples containing plain clottedblood are collected and sent for T3, T4, TSH estimation. The hormone estimation is done by chemiluminescence assay.
- ***Other investigations:***

- Hemoglobin, TLC, DLC, Erythrocyte sedimentation rate
- Random blood sugar
- Urine routine – sugar, albumin microscopy
- Blood urea
- Serum creatinine
- Lipid profile
- A standard 12 lead Electrocardiogram
- Two-dimensional transthoracic echocardiogram
- Chest radiograph

Statistical analysis

- "The collected data was entered with the help of Microsoft Excel spreadsheets version 2016. The data was presented in the form of tables and graphs for frequency analysis, to know the measures of central tendency and to study the distribution of the data."
- "Statistical analysis is done using IBM SPSS trial version 22.0 software."
- "Normally distributed variables were analyzed using parametric tests of significance (student"s t test)."
- "Association between categorical / nominal variables was tested using non-parametric tests (Chi-square test)."
- "The outcome of interest was calculated within 95% confidence limits. The differences between two observations was considered significant if the calculated P value was <0.05."

Results

Demographic characteristicsGender-wise distribution:

In the present study, we assessed the demographic features of the study subjects. We observed that majority of the subjects presented with hypothyroidism were females (82%), males were only 18%. The male to femaleratio was 1:4.5. The study population is mentioned in the table 1 and figure 4 given below.

Table 1: Distribution of study cases according to their gender

GENDER		**Frequency**	**Percent**
Valid	**MALE**	18	18.0
	FEMALE	82	82.0
	Total	100	100.0

cal presentation:

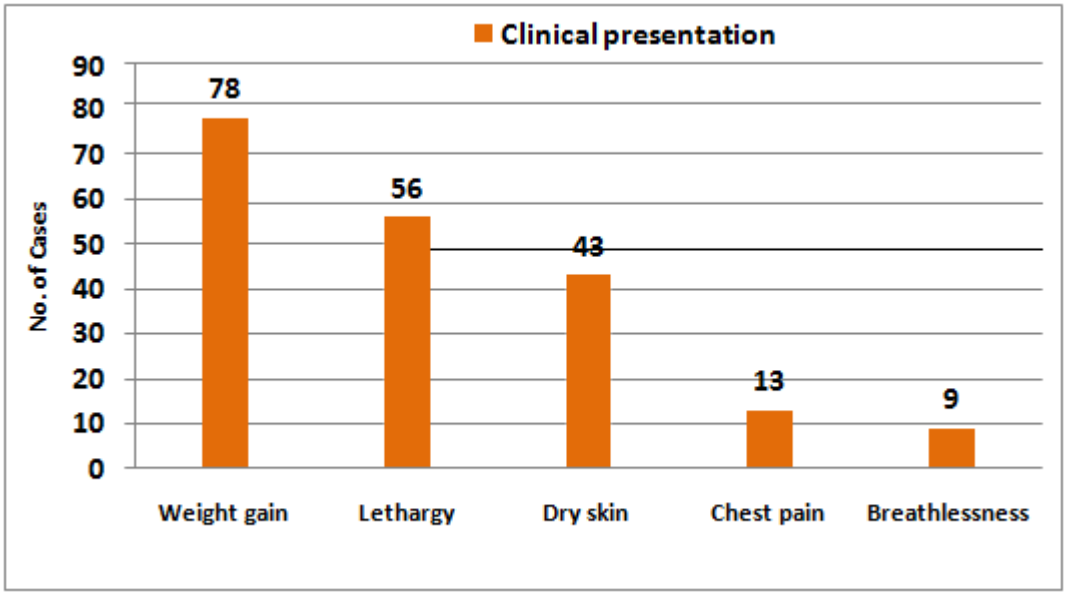
In the present study, we recorded the most common presenting symptoms of the cases of hypothyroidism. We observed that majority of cases presented with weight gain (78%), followed by lethargy among 56%, dry skin among 43%.Among cardiac complaints, 13% cases reported chest pain, 9% reported breathlessness and 5% cases presented with palpitations.

Table 3: Distribution of cases according to their clinical presentation

Clinical Presentation	**Number of cases**	**Percentage**
Weight gain	78	78
Lethargy	56	56
Dry skin	43	43
Chest pain	13	13

Breathlessness	9	9
Palpitations	5	5

Figure 6: Graphical presentation of study cases according to theirclinical presentation



Assessment thyroid function and classification:

In the present study, study cases are classified according to their various thyroid function parameters. We measured mean levels of serum TSH, Serum T3 and T4 hormones. The mean serum T3 levels were 65.47± 53.611 ng/dl, mean serum T4 levels were 6.63±9.037 micg/dl and the mean serum TSH levels were 31.58 ± 21.53 micIU/ml.

The cases are classified into mild, moderate and severe hypothyroidism basedon their serum TSH levels. We observed that majority of the cases were moderate hypothyroidism (49%), followed by mild hypothyroidism among 35% cases and 16% cases were presented with severe hypothyroidism.

Table 4: Analysis of serum T3, T4 and TSH levels

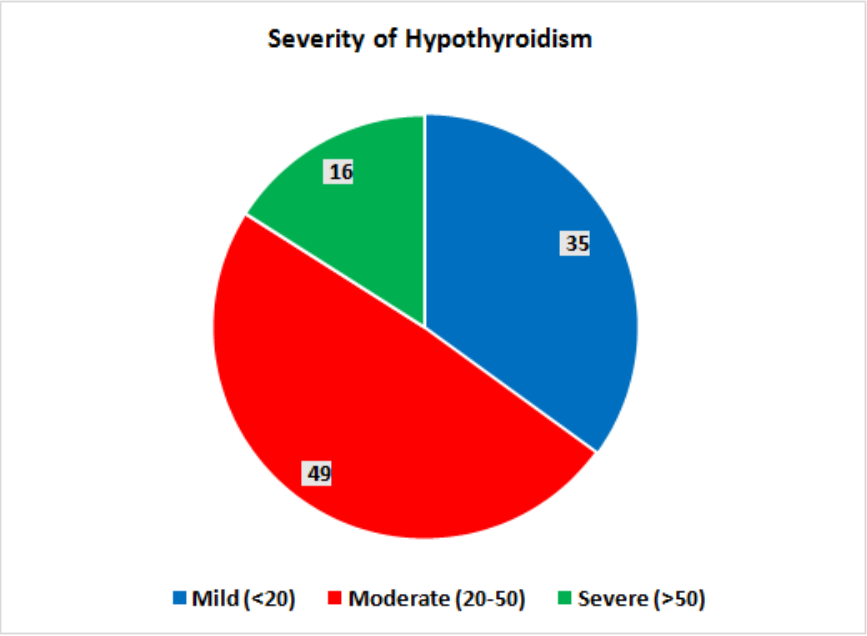
Thyroid function tests	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Serum T3 (ng/dl)	1	282	65.47	53.611

Serum T4 (micg/dl)	0.5	66	6.63	9.037
Serum TSH (micIU/ml)	5.30	99.78	31.5827	21.53458

Table 5: Severity of hypothyroidism

Severity of hypothyroidism (TSHlevels in micIU/ml)	**Number of cases**	**Percentage**
Mild (<20)	35	35
Moderate (20-50)	49	49
Severe (>50)	16	16
Total	100	100

Figure 7: Graphical presentation of severity of hypothyroidism



ISSN 2515-8260 Volume 09, Issue 01, 2022

Electrocardiographic findings in hypothyroidism:

In the present study, when we assessed various cardiac parameters (ECG parameters), we observed that the mean heart rate of the study subjects with hypothyroidism was 66.13± 9.36 per minute. Mean QT interval was 394 ±44.336 milliseconds. The detailed distribution of various cardiac parameters isgiven in the following table.

Atrial fibrillation was observed among 4 cases (4%). When we assessed the mean serum TSH levels, we observed that the mean level of serum TSH among the cases presented with AF was 54.80 ±35.90 micIU/ml, and the same among the cases without AF was 30.61 ±20.46. The difference was statisticallyfound to be significant (p-value is 0.013497).

Similarly when we assessed presence of low voltage among the cases of hypothyroidism, we observed that 6% cases presented with low voltage complexes in ECG, and their serum TSH level was significantly higher (64.11±24.34) as compared to those cases who did not presented with low voltage complexes in ECG. (The t-value is -4.11245. The p-value is 0.000041)

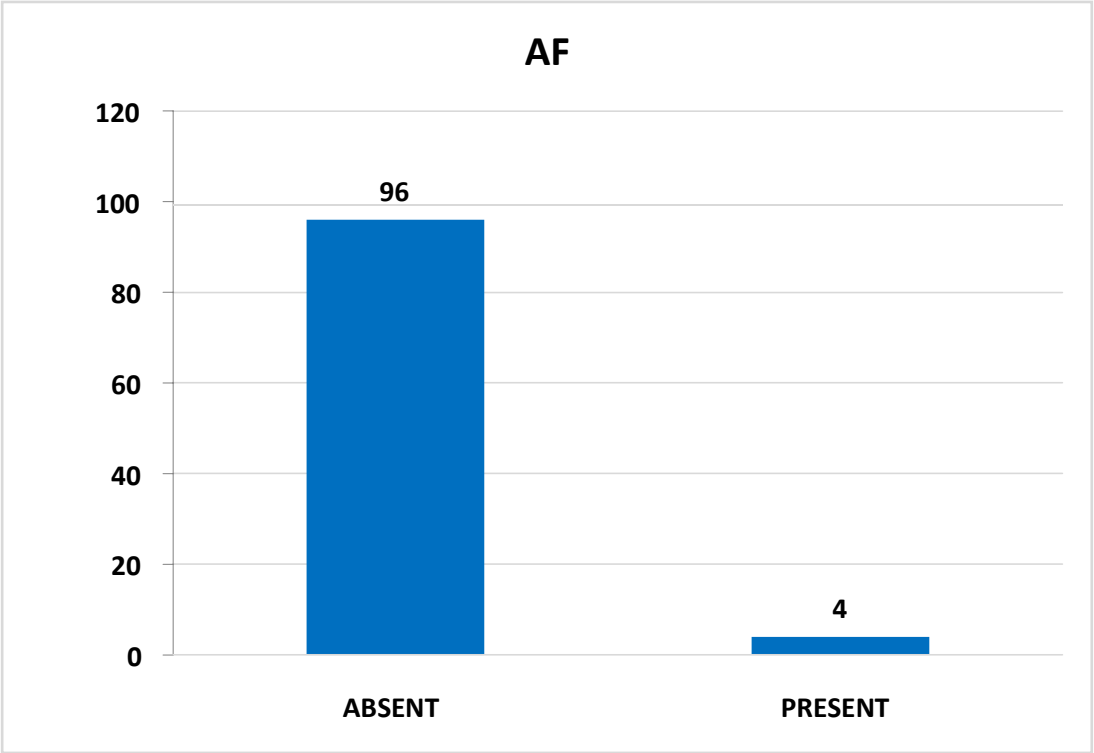
Table 6: Electrocardiographic findings

ECG findings	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Heart rate (per minute)	47	90	66.13	9.36
QT interval (milliseconds)	320	640	394.00	44.336

Table 7: Presence of atrial fibrillation

Atrial fibrillation		**Frequency**	**Percent**	**ean serumTSH levels (micIU/ml)**
No. of Cases				
Valid	**Absent**	96	96.0	30.61 ±20.46
	Present	4	4.0	54.80 ±35.90
	Total	100	100.0	---
Significance	**The t-value is 2.24531.** The **p-value is 0.013497**.			

Figure 8: Presence of atrial fibrillation



ST-T changes and blocks:

In the present study, ST-T segment changes were observed among 8% cases, whose mean serum TSH level was 60.15±31.05, which was significantly greater as compared to serum TSH values of those who did not presented withST-T changes (29.09±18.77), [**The t-value is 4.23403. The p-value is 0.000026**]

In the present study, we did not found any case of LBBB or RBBB.

Table 9: Presence of ST-T changes

ST-T changes		**Frequency**	**Percent**	**lean serumTSH levels**
Valid **No. of Cases**	**Absent**	92	92.0	29.09±18.77
	Present	8	8.0	60.15±31.05
	Total	100	100.0	---
Significance	**The t-value is 4.23403. The p-value is 0.000026**			

Figure 10: Presence of ST-T changes

ISSN 2515-8260 Volume 09, Issue 01, 2022

Two-dimensional transthoracic echocardiographic findings: Systolic and diastolic dysfunction:

In the present study, we assessed the study subjects according to presence of systolic dysfunction. We observed that 2% cases reported with severe degree of systolic dysfunction with ejection fraction <30% and 3% cases with moderate degree of dysfunction (EF 31-45%), the mean serum TSH levels among moderate and severe systolic dysfunction cases was greater as compared to others.

Similarly 18% cases presented with grade I diastolic dysfunction (mean TSH value 29.64± 22.90 micIU/dl), and 2% cases presented with grade II diastolic dysfunction (mean TSH value 67.01± 19.62 micIU/dl.)

Table 10: Presence of systolic dysfunction

Systolic dysfunction		**Frequency**	**Percent**	**Mean serum TSH levels**
Valid	**Absent**	**97**	**97**	**29.07±20.0**
	Moderate	**3**	**3**	**65.94±23.73**
	Severe	**2**	**2**	**99.23± 0.77**
	Total	**100**	**100.0**	**---**

Significance	**The t-value is 5.87695. The p-value is < 0.00001**

Table 11: Presence of diastolic dysfunction

Diastolic dysfunction		**Frequency**	**Percent**	**Mean serum TSH levels**
Valid	**Absent**	**80**	**80.0**	**31.13±20.74**
	Grade I	**18**	**18.0**	**29.64±22.901**
	Grade II	**2**	**2.0**	**67.01±19.62**
	Total	**100**	**100.0**	**---**
Significance	**The t-value is 0.41566. The p-value is 0.339285.**			

Presence of pericardial effusion:

In the present study, we classified the cases based on presence or absence of pericardial effusion among cases of hypothyroidism. We observed that 6% cases presented with pericardial effusion. We also compared the serum TSH levels among them and observed that the cases presented with pericardial effusion had significantly greater serum TSH levels as compared to others (67.07±40.68). [The t-value is 4.56184. The p-value is < 0.00001]

Table 13: Presence of pericardial effusion

Pericardial effusion		**Frequency**	**Percent**	**Mean serum TSH levels**
Valid	**Absent**	94	94.0	29.31±17.83
	Present	6	6.0	67.07±40.68
	Total	100	100.0	---

Significance	**The t-value is 4.56184. The p-value is < 0.00001.**

Chest radiograph findings:

In the present study, we assessed the study subjects according to their chest radiograph findings. We observed that 6 cases (6% cases) were diagnosed to have cardiomegaly on chest radiograph.

Table 14: Presence of cardiomegaly

CARDIOMEGALY		**Frequency**	**Percent**
Valid	**NO**	94	94.0
	YES	6	6.0
	Total	100	100.0

DISCUSSION

Hypothyroid individuals often exhibit a wide variety of nonspecific symptoms and indicators in the clinic. Therefore, the key to a prompt diagnosis of hypothyroidism is a high index of suspicion. Patients with hypothyroidism are at a higher risk of developing functional cardiovascular abnormalities, which contributes to their elevated cardiovascular risk. Subclinical and overt hypothyroidism have a similar pattern of cardiovascular abnormalities, which suggests that even a little shortage in thyroid hormone might have an impact on cardiovascular health. This is why we decided to investigate the link between the severity of hypothyroidism and the development of cardiovascular problems in the patients who presented themselves to the general medicine clinic at our academic medical centre.

ECG FINDINGS IN HYPOTHYROIDISM

In the present study, when we assessed various cardiac parameters (ECG parameters), we observed that the mean heart rate of the study subjects with hypothyroidism was 66.13± 9.36 BPM. Mean QT interval was 394 ± 44.336 milliseconds. In the present study, bradycardia was found among 25% cases. **K.Ramesh et al** in their study noted that bradycardia was found in 40% of patients.[112]

ATRIAL FIBRILLATION

Atrial fibrillation was observed among 4 cases (4%). When we assessed the mean serum TSH levels, we observed that the mean level of serum TSH among the cases presented with AF was 54.80 ±35.90 micIU/dl, and the sameamong the cases without AF was 30.61 ±20.46 micIU/dl. The difference was statistically found to be significant (p-value is 0.013497).

LOW VOLTAGE COMPLEXES IN ECG

Similarly when we assessed presence of low voltage among the cases of hypothyroidism, we observed that 6% cases presented with low voltage ECG, and their serum TSH level was significantly higher (64.11±24.34) as compared to those cases who did not presented with low voltage ECG. (The t-value is
-4.11245. The p-value is 0.000041).

Bijaya Kumar Behera et al[111]**,** in their study reported that low voltage complexes in ECG were found 60% of patients, out of which 6 (10%) were males, 30% were females. Similarly, 15% males had T-inversion in V3 - V6 leads and RBBB was seen in 29% patients. Their findings were greater than our study. **K.Ramesh et al** in their study noted that Low voltage complexes were seen in 35%.[112]

ST-T CHANGES AND BLOCKS

In the present study, ST-T segment changes were observed among 8% cases, whose mean serum TSH level was 60.15±31.05 micIU/dl, which was significantly greater as compared to serum TSH values of those who did not presented with ST-T changes (29.09±18.77), [The t-value is 4.23403. The p-value is 0.000026]. In the current study, we did not found any case of LBBB or RBBB. **K.Ramesh et al** in their study reported that the LBBB and RBBB found in 5% and 7.5%.[112]

The study by **Varma R et al,** showed the prevalence of effusion to be 22.75% to 45%. Pericardial effusion is reported to occur in 30% to 80% of patients with hypothyroidism. **K.Ramesh et al**[112] in their study noted Pericardial effusion seen in 27.5% cases.

In present study, patients with higher serum TSH levels (severe hypothyroidism) had more number of patients with cardiovascular involvement. Involvement of various systems in hypothyroidism depends on duration, onset and severity of hypothyroidism.

SUMMARY

We studied the clinical presentation of the cases, where we observed that majority of cases presented with weight gain, lethargy, dry skin, and rarely the cardiac complaints.

After studying the thyroid function of the patients, we observed that majority of the cases were of moderate hypothyroidism (49%), followed by mild hypothyroidism among 35% cases and 16% cases were presented with severe hypothyroidism. The mean serum T3 levels of the [patients were 65.47± 53.611 ng/dl, mean serum T4 levels were 6.63±9.037 micg/dl and the mean serum TSH levels were 31.58 ± 21.53 micIU/dl.

In the present study, bradycardia was found among 25% cases. We observed significantly more serum TSH levels among the cases presented with atrial fibrillation as compared to those who did not presented with AF.

Similarly, 6% cases presented with low voltage complexes in ECG. We observed significantly more serum TSH levels among the cases presented with low voltage complexes in ECG as compared to those who did not presented with it.

We also compared the serum TSH levels among them and observed that the cases presented with pericardial effusion had significantly greater serum TSH levels as compared to others. Relatively low incidence of pericardial effusion may be due to selection of new hypothyroid cases.

More individuals with cardiovascular involvement were found in the current investigation among those with higher blood TSH levels (severe hypothyroidism). How long you've had hypothyroidism, when it started, and how severe it is all have a role in how your body reacts.

CONCLUSION

The present study concludes that the hypothyroidism was often among females. The weight gain, lethargy and dry skin were the commonest presenting symptoms in the cohort of hypothyroid patients. Chest pain, breathlessness and palpitations were the commonest cardiac complaints

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