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Cardiovascular Interdependence on Hypothyroidism

Dr. Dany P. John1 ,Dr. Desai Jabbar V.2 Dr. Anil Bhattad3 Assistant prof.,
Department of Medicine, Krishna Institute of Medical Sciences, Krishna Institute of Medical Sciences Deemed to be University ,Karad
Email :- Danyjohn411425@gmail.com

Abstract

During the third week of gestation, the thyroid gland begins to form on the floor of the rudimentary pharynx. The thyroglossal duct carries the gland from its origin at the foramen caecum at the base of the tongue to its eventual resting place in the neck. These cysts of the thyroglossal duct and the unusual ectopic position of thyroid tissue at the base of the tongue (lingual thyroid) are both explained by this anatomical trait. Synthesis of thyroid hormone typically starts during the 11th week of pregnancy.

Thyroid follicular cells form the follicles seen in a fully developed thyroid gland, and the colloid they release is a proteinaceous fluid rich in thyroglobulin.[9]

Key Words: Thyroid, Pharynx, gestation, foramen caecum, ectopic, lingual, gestation,

Introduction

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.

Since thyroid hormones have an impact on almost every major metabolic route, thyroid illness is often accompanied by a wide range of metabolic disorders. The basal metabolic rate is controlled by thyroid hormones, which in turn affect protein, carbohydrate, and lipid metabolism. Both direct and indirect effects are possible, the latter occurring via the regulation of hormones like insulin and catecholamines.[2] The effect of thyroid hormones on every step of lipid metabolism, leading to a wide range of quantitative and/or qualitative changes in triglycerides, phospholipids,

cholesterol, and other lipoproteins, culminates in dyslipidemia, a common metabolic abnormality in patients with both overt and subclinical forms of thyroid disease.[3]

The increased risk of cardiovascular disease in those with thyroid illness may be attributed to dyslipidemia and other metabolic disorders, as well as the hemodynamic changes generated by thyroid hormone.[4–7]

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. Functional systolic and diastolic dysfunction, overt failure, and coronary artery disease are all forms of cardiac dysfunction.

Thus, the need of this study is to assess the CVS parameters in new hypothyroid patients by electrocardiogram and two-dimensional transthoracic echocardiography. The completely reversible nature of these complications is well known.

Hence this study aims at studying the cardiac manifestations of hypothyroidism,thereby reassessing the need for early recognition and more aggressive management of the disease, aiming at preventing the aforementioned complications.

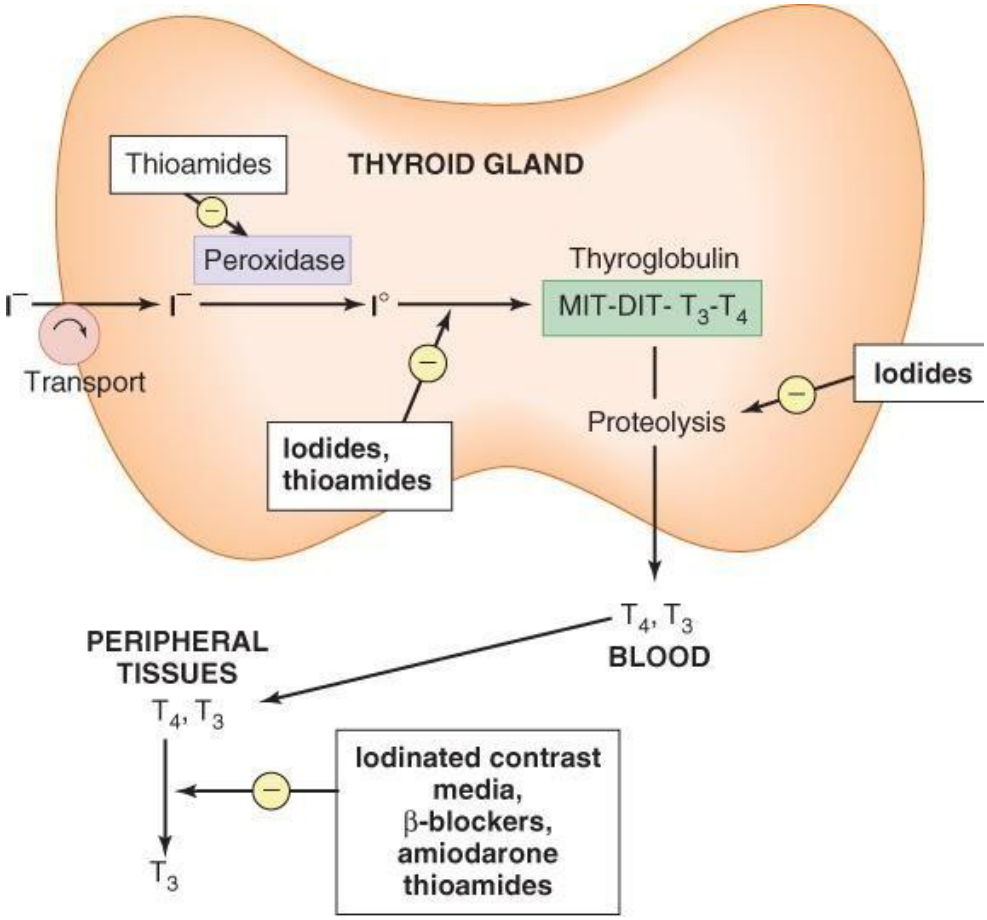
Review of Literature Tissue metabolism and development are profoundly affected by the thyroid gland's activity, which in turn has consequences for other body systems. In this chapter, we explore the root causes and overall effects of hyperthyroidism, hypothyroidism, and other kinds of thyroid illness, with a focus on the impact of thyroid hormones on the cardiovascular system.

Wharton, in 1656, is credited with giving the thyroid gland its name (from the Greek thyreos, shield, and eidos, shape), but the idea that it serves an endocrine role wasn't put forth until over 200 years later. Following this, the initial descriptions of the clinical illnesses affecting the thyroid surfaced, and they are listed below in chronological sequence of increasing appreciation. Hashimoto disease in 1912; subacute (de Quervain) thyroiditis in 1936; the structure of thyroxine (T4) in 1926; identification of triiodothyronine (T3) in 1952; thyroid cancer in 1811; diffuse toxic goitre by Parry in 1825, Graves in 1835, and Von basedow in 1840; cretinism in 1871; myxedema in 1874; thyroidectomy for the treatment

During the third week of gestation, the thyroid gland begins to form on the floor of the rudimentary pharynx. The thyroglossal duct carries the gland from its origin at the foramen caecum at the base of the tongue to its eventual resting place in the neck. These cysts of the thyroglossal duct and the unusual ectopic position of thyroid tissue at the base of the tongue (lingual thyroid) are both explained by this anatomical trait. Around the eleventh week of pregnancy, thyroid hormone production typically starts.

Thyroid follicular cells form the follicles seen in a fully developed thyroid gland, and the colloid they release is a proteinaceous fluid rich in thyroglobulin.[9]

Figure 1: Synthesis and transport of thyroid hormones



1.1. Thyroid hormone transport and metabolism:

The thyroid gland secretes T4 at a rate at least 20 times higher than T3. Both hormones are transported through the bloodstream attached to various plasma proteins such thyroxine binding globulin (TBG), transthyretin (TTR; previously known as thyroxine-binding prealbumin, or TBPA), and albumin. Serum-binding proteins' roles include boosting the amount of hormone in circulation, slowing the rate at which it is cleared from the body, and perhaps modulating the amount of hormone delivered to certain tissues. Since TBG has a far higher affinity for T4 than T3, it transports over 80% of the bound hormones despite its modest concentration (1–2 mg/dL). Albumin has a high plasma content but a modest affinity for thyroid hormones, binding up to 10% of T4 and 30% of T3. The normal concentrations of free hormones are what the TTR homeostatic mechanisms that control the thyroid axis are aiming for.

HYPOTHYROIDISM AND CARDIOVASCULAR RISK MARKERS:

"Elevated levels of total cholesterol, LDL cholesterol, and apolipoprotein B are well documented features of overt hypothyroidism".[66] "Early studies in humans with hypothyroidism, using isotopically labelled LDL, demonstrated a prolongedhalf-life of LDL cholesterol because of decreased catabolism, an effect that wasreversible with T4 therapy".[67] "Additional data in human fibroblasts verified that the T3-induced increase in LDL degradation was mediated through an increase in LDL receptor number, without any change in the affinity of LDL for its receptor. A specific effect of thyroid hormone on the LDL receptor was suggested by a lack of T3 effect on LDL concentration in cultured cells withoutLDL receptors".[68]

Consistent with these results, an in vivo research conducted on a hypothyroid lady found that her receptor-mediated LDL catabolism was lower than that of euthyroid controls, but significantly improved once she began taking T4..[69]

On the other hand, there is currently substantial evidence that suggests subclinical hypothyroidism is not linked to elevated levels of homocysteine in the blood. Subclinical hypothyroidism has been linked to increased homocysteine levels,

but three case-control studies have shown no such association. And even after treating subclinical hypothyroidism, Christ-Crain et al. reported no significant decrease in homocysteine levels. Even in non-diabetic people, insulin resistance and the metabolic syndrome have been demonstrated to be risk factors for cardiovascular disease. Bakker et al. hypothesised that substantially lower thyroid hormone levels would magnify the increased cardiovascular risk associated with insulin resistance, even though hypothyroidism does not seem to induce insulin resistance. TSH concentration was not related with any change in LDL level in insulin-sensitive people, whereas the opposite was true for insulin-resistant participants.[80-82]

MATERIALS AND METHODS

Type of study : Cross sectional descriptive study

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

Sample size: Convenient sampling technique was used in the present study 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:

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

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

Cases giving informed written consent.

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

Case selection criteria that do not apply:

A. People who already have heart disease

B. Patients suffering from endocrine disorders, such as those with chronic obstructive lung disease, severe anaemia, or diabetes mellitus.

C. People who use drugs that affect the thyroid, such as beta blockers, lithium, oral contraceptives, steroids, and alcohol.

Informed consent: the patients fulfilling the selection criteria were briefed about the nature of study after obtaining a written informed consent.

Ethical clearance: this study was approved by protocol and ethics committee of KIMS deemed to be university.

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.
- 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.
- 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

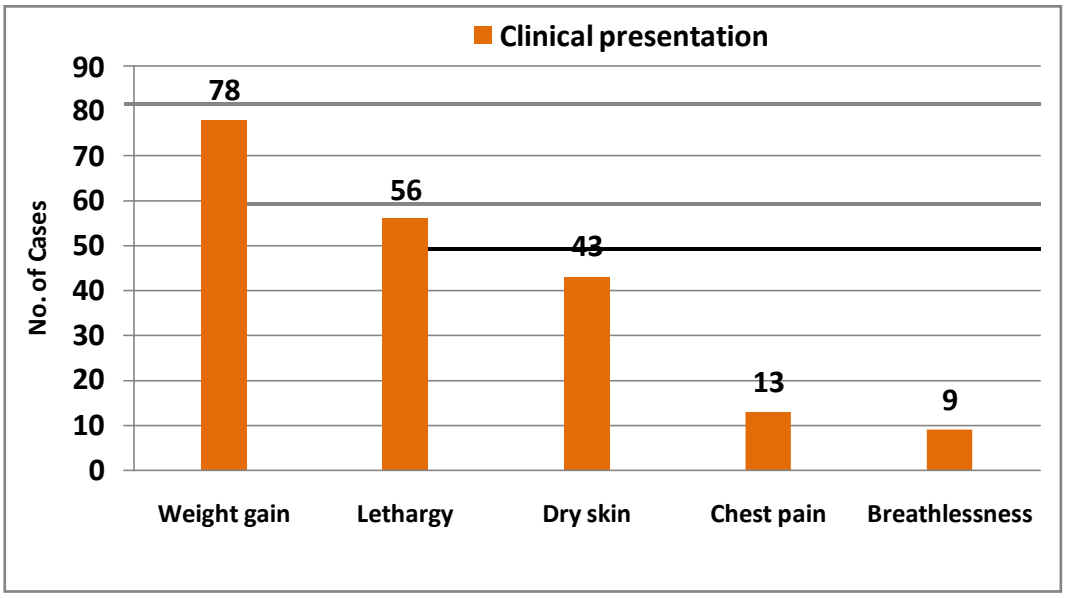
- Using Microsoft Excel 2016 spreadsheets, the gathered information was inputted. The information was laid up in tables and graphs so that its frequency could be examined, its core tendencies could be determined, and its dispersion could be examined.
- Statistical analysis is done using IBM SPSS trial version 22.0 software.
- Parametric statistical tests (the student's t test) were used for the analysis of normally distributed data.
- Non-parametric tests were used to examine the relationship between nominal and categorical variables (Chi-square test).
- Within 95% confidence intervals, the result of interest was computed. If the estimated P value of a statistical test between two observations was less than 0.05, then the difference between the two was regarded to be significant.

RESULTS

Table 1: 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 2: Graphical presentation of study cases according to their clinical 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.

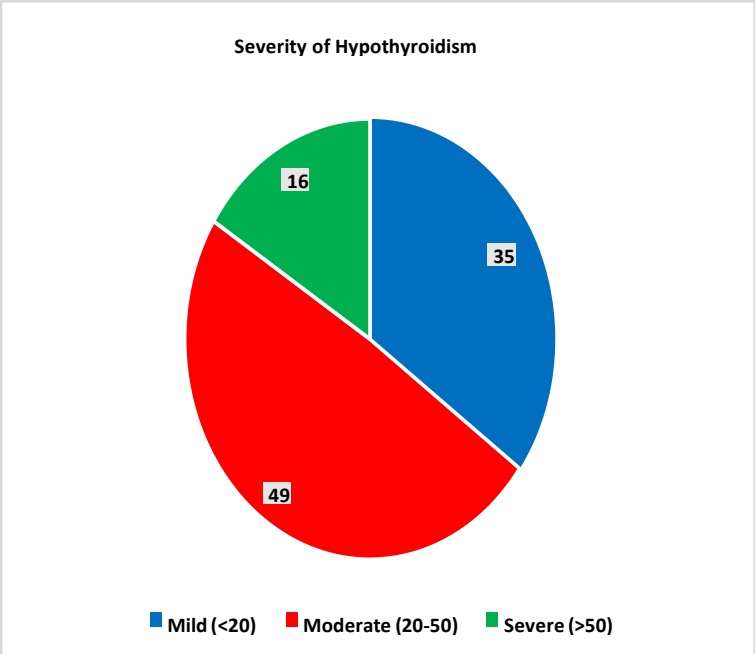
Table 2: **Analysis of serum T3, T4 and TSH levels**

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 3: Severity of hypothyroidism

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

***Figure 3*: Graphical presentation of severity of hypothyroidism**



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 sameamong 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 4: **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 5: Presence of atrial fibrillation

Atrial fibrillation		**Frequency**	**Percent**	**Mean serum TSH levels (micIU/ml)**
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**.			

Table 6: **Presence of ST-T changes**

ST-T changes		**Frequency**	**Percent**	**Mean serum TSH levels**
Valid	**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**			

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 7: **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 8: **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.**			

CLINICAL 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.

Bijaya Kumar Behera et al, in their study reported that "Cardiovascular symptoms were seen only in 12 patients (20%) which includes effort intolerance in 6 (10%), chest pain, breathlessness and palpitation in 2 patientseach 3.3%".[111]

According to **K.Ramesh et al, "**the most common symptoms in their study wereof weight gain (72.5%), lethargy (65%) and dry skin (62.5%)." [112]

SYSTOLIC AND DIASTOLIC DYSFUNCTION

In the present study, we assessed the study subjects according to presence ofsystolic dysfunction. We observed that 2% cases reported with severe degree of systolic dysfunction and 3% cases with moderate degree of dysfunction, themean 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), and 2% cases presented with grade II diastolic dysfunction (mean TSH value 67.01± 19.62)

According to research by Bijaya Kumar Behera et al[(111)] diastolic dysfunction was present in 26.6% of patients and systolic dysfunction was present in 6.6% of patients. Research conducted by Varma R et al [(115)] The prevalence of diastolic dysfunction was shown to be 27. Patients have systolic dysfunction at a rate of 6.67 percent. Forfar, et al [(116)], Patients with hypothyroidism have been reported to have decreased systolic function indices. Although Ridge et al. have suggested that the comparatively advanced ages of the patients in these trials may be at play here, the effect size is still rather tiny. With regard to systolic function, they saw no change in their younger patients (aged 20-48years). Fouron et al.,

Grossman et al., and Verma R et al. all came to similar conclusions, reporting no systolic dysfunction in their hypothyroid individuals. There was no systolic dysfunction in the study by Rawat B. and Satyal A. published in the KUMJ (2003), volume 2. In their research, K.Ramesh et al. found that 27.5 percent of participants had diastolic dysfunction. [112]

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]. Relatively low incidence of pericardial effusion may be due to selection of new hypothyroid cases.

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

Bijaya Kumar Behera et al[111], in their study reported that the Diastolic dysfunction and pericardial effusion was found in 26.6% cases.

Summary and Conclusions

It is well documented that the hypothyroidism is related to an increased risk of functional cardiovascular abnormalities. Hence the present study was conducted to study association between severity of hypothyroidism and occurrence of cardiovascular complications among the cases presented with hypothyroidism in the department of general medicine, in a tertiary healthcare teaching institute.

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 withlow voltage complexes in ECG as compared to those who did not presented with it.

In the current study, ST-T segment changes were observed among 8% cases, whose mean serum TSH level was significantly greater as compared to serumTSH values of those who did not presented with ST-T changes. In the present study, we did not found any case of LBBB or RBBB.

We observed that 2% cases reported with severe degree of systolic dysfunctionand 3% cases with moderate degree of dysfunction, 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, and 2% cases presented with grade II diastolic dysfunction.

We observed that 10% cases had increased IVS thickness. We compared the mean serum TSH levels among the cases with increased IVS thickness which was found significantly greater as compared to those cases with normal IVS thickness.

Electrocardiograms often showed bradycardia, low voltage complexes, and ST-T alterations. Most often seen abnormalities on a standard transthoracic echocardiography were pericardial effusion, diastolic dysfunction, and thickened interventricular septum. Higher levels of TSH were associated with an enhanced involvement of the cardiovascular system in the current investigation. Therefore, it follows that everyone who has been given a diagnosis of hypothyroidism should have a cardiac screening.

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