A STUDY ON PREVALENCE OF PERICARDIAL EFFUSION IN NEWLY DIAGNOSED ADULT HYPOTHYROID PATIENTS

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfilment of the regulations
for the award of the degree of

M.D. BRANCH – I
GENERAL MEDICINE

MADRAS MEDICAL COLLEGE
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI, INDIA

FEBURARY 2008

CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON PREVALENCE OF PERICARDIAL EFFUSION IN NEWLY DIAGNOSED ADULT HYPOTHYRIOD PATIENTS"** submitted by **Dr. G. ABIRAMI,** appearing for Part II M.D. Branch I General Medicine Degree examination in March 2008 is a bonafide record of work done by her under my direct audience and supervision in partial fulfilment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled "**A STUDY ON PREVALENCE OF PERICARDIAL EFFUSION IN NEWLY DIAGNOSED ADULT HYPOTHYROID PATIENTS"** is done by me at Madras Medical College & Govt. General Hospital, Chennai during 2006-2007 under the guidance and supervision of **Prof.M.JUBLIEE, M.D.**

The dissertation is submitted to "The Tamilnadu, Dr. M.G.R. Medical University" towards the partial fulfilment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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ACKNOWLEDGEMENT

I would like to express my sincere gratitude to my beloved Professor and Director, Institute of Internal Medicine **Prof. Thirumalai Kolunthu Subramanium, M.D.,** for his guidance and encouragement.

With extreme gratitude, I express my indebtedness to my beloved Chief **Prof. M. Jubilee, M.D.,** for her motivation, advice and valuable criticism, which enabled me to complete this work.

I am extremely thankful to Assistant Professors of Medicine **Dr. Kani Sheik Mohammed, M.D.,** and **Dr. Sivakumar, M.D.,** for their co-operation and guidance.

I would always remember with extreme sense of thankfulness the co-operation and criticism shown by my Postgraduate colleagues.

I am immensely grateful to the generosity shown by the patients who participated in this study. If at all, this study could contribute a little to relieve them from their suffering I feel that I have repaid a part of my debt.

CONTENTS

INTRODUCTION

Although association of pericardial effusion with Hypothyroidism is a known entity for many decades, various studies report varying incidences. The purpose of the present study is to enlighten the already established association and to observe the incidence and severity of pericardial effusion, its relation to duration and severity of hypothyroidism. The unique feature of “Hypothyroid” pericardial effusion is that unlike, other exudative effusion, it disappears with medical treatment without any residual sequelae.

The terms Myxedema and hypothyroidism are often used interchangeably. But the latter is more inclusive, encompassing all degrees of hypo metabolism from normal to complete atherosis. Myxedema is a particular syndrome, a florid hypothyroidism occupying the lower end of this spectrum.

The first known description of pericardial effusion in a hypothyroid patient dates back to 1918 . Since then, several publications have reported on the association between hypothyroidism and pericardial effusion, and even other serous effusions . Pericardial effusion is considered the most frequent cardiovascular complication

of hypothyroidism, with a prevalence estimated to be between 30% and 80%.

Historical resume

The functions and diseases of the thyroid is well documented in literature over centuries and important aspects are given below in brief

- The earliest description of the thyroid was given by Galen in his devoice.
- In 1543,Vesalius gave a full description of the gland
- In 1656, Wharton named the organ as “Thyroid” or “Oblong Shield”
- In 1874, Gull first described the clinical syndrome of hypothyroidism
- In 1878, W.M.ORD coined the word Myxedema
- In 1883, Reverdius and Kocher reported the similarity between Myxedema and the clinical picture that developed after successful removal of the thyroid
- In 1896, Boumann described the association of iodine with the working of the Thyroid.
- In 1912, Hashimoto described chronic thyroiditis

- In 1915, Kendall crystallised L-Thyroxin from alkaline hydrolysates of thyroid tissues

ANATOMY

The thyroid gland is the largest endocrine gland in human beings, weighing about 20g in an adult. The Thyroid is so called because of its topographic relationship to the laryngeal cartilage, which looks like a Greek shield.

The thyroid gland is derived from the endoderm at the base of the tongue. The gland is closely affixed to the anterior and lateral aspects of the trachea by loose connective tissue. The upper margin of the isthumus generally lies just below the cricoid cartilage. The functioning unit is the lobule, which consists of 20-40 follicles, which are lined by cubical epithelium. The resting follicle contains colloid in which thyroglobulin is stored.

PHYSIOLOGY

Thyroid Hormone Bio- Synthesis

The thyroid hormone biosynthesis can be considered as occurring in three sequential stages

i. Active transparent of iodine into the gland

ii. Oxidation if iodine and iodination by the oxidized form of tyrosyl residues within thyroglobulin to yield hormonally inactive iodotyrosines

iii. Coupling of iodotyrosines to form the hormonally active iodothyronines (T_3 and T_4)

Storage and release of hormones:

The thyroid gland has a large store of thyroid hormone. The organic content in the thyroid is constituted as follows. MIT: 17-20%, DIT: 24-42%, T3>35%, T4 5-8%. The T4:T3 ration maybe greater than 10:1.

Thyroglobulin is the storage form of thyroid hormone and enters blood via lymphatics. T3 and T4 enter the blood directly after being liberated from thyroglobin by proteolytic cleavage within the follicular cell. Iodotyrosines liberated from thyroglobulin are subject to the action of micro-somal Iodotyrosine dehalogenase, an NADPH dependent enzyme and TSH actively enhances this enzyme.

Transport of thyroid hormones

A wide variety of iodothyroninies and their metabolic derivatives exist in plasma. Of these T4 is highest in the concentration and is the only one arising solely by direct secretion from the thyroid gland. In normal person 20-40% of T3 is secreted from the gland but 60-80% of T3 in the plasma is derived from peripheral tissues by the enzymatic removal of a single iodine atom from T4. The other iodothyronines like T3 and 3.3'-T2 are generated entirely in the peripheral tissues from T4 and T3.

Extra-cellular binding proteins

Upon entering the blood the major secretary products T4 and T3 of the normal thyroid gland bound in a firm but reversible bond to several proteins, which are synthesized in the liver. T4 is mainly associated with the thyroid binding, Pre-albumin (TBPA) and also to albumin. Thyroid binding globulin (TBG) is a glycoprotein with molecular wt 54,000 and its concentration in plasma is 2 µg/dl, which is capable of binding about 20ug of T4.

TBPA exists in part as a complex with retinol binding protein. Its concentration in plasma is about 25µg/dl, which binds about 200µg

of T4. TBG is responsible for 77% of transport of T4 and with the serum T4 concentration is the major determinant of free T4. In normal serum free T4 is ~0.03% of the total T4, which is abut 2µg/dl.

AIM OF THE STUDY

- To study the prevalence of pericardial effusion in adult hypothyroid patients
- To find a correlation between severity of disease and presence of pericardial effusion
- To find the risk factors predisposing patients with hypothyroidism to develop pericardial effusion

REVIEW OF LITERATURE

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. It usually is a primary process in which the thyroid gland produces insufficient amounts of thyroid hormone. It can also be secondary, that is lack of thyroid hormone secretion due to the failure of either adequate thyroid-stimulating hormone [TSH]) secretion from the pituitary gland or thyrotropin-releasing hormone (TRH) from the hypothalamus (secondary or tertiary hypothyroidism). The most common cause is autoimmune thyroid disease (Hashimoto thyroiditis)[1].

Subclinical hypothyroidism, also referred to as mild hypothyroidism, is defined as normal serum free T4 levels with slightly high serum TSH concentration.

According to a survey by Jayarama, K. S. et al the prevalence of hypothyroidism in India is 0.071%.[2]

In a study by Kajantie E, Phillips DI, Osmond C, Barker DJ, Forsen T and Eriksson JG on spontaneous hypothyroidism in adult women is predicted by small body size at birth and during childhood., hypothyroidism is more common in women with small body size at birth and low body mass index during childhood.[3]

Iodine deficiency as a cause of hypothyroidism is more common internationally. The prevalence is reported by Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, et al. Hollowell JG, Staehling NW, Flanders WD, et al. in a study on Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III) was 2-5%, increasing to 15% by age 75 years[4].

Community studies use slightly different criteria for determining hypothyroidism; therefore, female-to-male ratios vary. A review article by Shikha Bharaktiya states that generally, thyroid disease is much more common in females than in males, with reports of prevalence 2-8 times higher in females[5].

The frequency of hypothyroidism, goiters, and thyroid nodules increases with age. In the same review article by Shikha Bharaktiya it was found that hypothyroidism was most prevalent in elderly populations, with 2% to as much as 20% of older age groups having some form of hypothyroidism.[5] In the Framingham study, thyroid function was assessed in adults older than 60 years. The study found hypothyroidism (TSH >10 mIU/L) in 5.9% of women and 2.4% of men[5].

In a study by Kreisman SH, Hennessey JV et al on 'Consistent reversible elevations of serum creatinine levels in severe hypothyroidism', metabolic abnormalities associated with hypothyroidism included anemia, dilutional hyponatremia, hyperlipidemia, and reversible increase in creatinine.[6]

Cardiac involvement in myxedema was first described by Zondek[7] in 1918. The association between pericardial effusion and hypothyroidism was first brought out by Freeman in 1934[7.]

Shikha Bharaktiya in the review article explains the cardiac involvement in hypothyroidism as follows. In hypothyroidism the cardiac output at rest is decreased because of reduction in both stroke volume and heart rate, reflecting loss of the inotropic and chronotropic effects of thyroid hormones. Peripheral vascular resistance at rest is increased and blood volume is reduced. These hemodynamic alterations result in narrowing of pulse pressure prolongation of circulation time and decrease in blood flow to the tissues. The decrease in cutaneous circulation is responsible for the coolness and pallor of skin, and the sensitivity to cold. In most tissues, the decrease in blood flow is proportional to the decrease in oxygen consumption, so that the mixed arterio-venous oxygen difference remains essentially normal. The hemodynamic alteration at rest resembles those of congestive heart

failure, but cardiac output increases and peripheral vascular resistance decreases in normally response to exercise[5].

In thyroprivic hypothyroidism the heart is enlarged and the heart sounds are decreased in intensity. These findings are largely due to effusions in the pericardial sac of fluid rich in protein and mucoploy saccharides. Angina pectoris is uncommon in hypothyroidism and occasionally disappears when the euthyroid state is restored. Hypercholesterolemia of hypothyroidism predisposes to coronary atherosclerosis only in the presence of hypertension.

Crawford W.Adams in his study showed that the electrocardiographic changes include sinus bradycardia, prolongation of the PR interval, low amplitude of P wave and QRS complex, alterations of the ST segment and flattened or inverted T waves in hypothyroidism. Pericardial effusion is probably responsible in part for ECG changes. Rarely complete heart block may be present. But this disappears when hypothyroidism is treated. But this disappears when hypothyroidism is treated. Systolic time interval is altered, the pre-ejection period is prolonged and the ratio of pre-ejection period to left ventricular ejection time is increased.

Tajiri J, Morita M, Higashi K, Fujii H, Nakamura N, Sato T [21] et al in order to clarify the cause of low voltage QRS complex seen on ECG (low voltage), thyroid hormones, LDH isozyme and pericardial effusion (PE) studied 39 patients with primary hypothyroidism. Low voltage and PE were found in 12 of 39 (30.8%) and 12 of 27 (44.4%), respectively. Serum T4 in patients with low voltage (Group 1) was significantly lower than that in patients without low voltage (Group 2) (T4 1.4 +/- 1.7 vs 2.8 +/- 2.3 micrograms/dl, p less than 0.05). Group 1 had a higher incidence of large amounts of PE than Group 2 (6/8 vs 1/19, p less than 0.002). However, there was no significant difference in thyroid hormone levels between patients with and without PE. No significant difference in LDH isozyme pattern was found among the groups. Low voltage without PE was found in only one patient. Two patients with low voltage and PE demonstrated that inspite of the presence of large PE, low voltage improved after thyroid replacement therapy. By multi-variate analysis, low voltage was related to large PE, patient age and low T4 levels. From these results, it was suggested that in hypothyroidism low voltage was brought about by a combination of both severe thyroid hormone deficiency and large PE. In addition, elderly patients over 60 years had low voltage more frequently than did patients under 59 years.

Mancuso L, Lo Bartolo G, Iacona MA, Bondi F, Marchi S et al conducted a study on - Echocardiography in primary hypothyroidism. Echo cardio graphic studies have revealed a high frequency of asymmetrical septal hypertrophy and apparent obstruction of the left ventricular outflow tract, suggesting idiopathic hypertrophic subaortic stenosis [8] 25 patients affected by Primary Hypothyroidism and a control group of 25 subjects were studied with M-mode and Two-dimensional echocardiography. In hypothyroid patients mean left ventricular and aortic root dimensions were normal compared to control subjects. Pericardial effusion was found in 22 out of 25 patients (88%). Septal hypertrophy was found in 12 hypothyroid patients (48%), only in 3 out of these 12 patients left ventricular posterior wall hypertrophy was found. A moderate left atrial enlargement was found in 7 out of 25 hypothyroid patients. Two-dimensional echocardiography revealed an uniform degree of parietal hypertrophy from the basal segments to the cardiac apex. Therefore the main echocardiographic findings in hypothyroidism are: presence of pericardial effusion and asymmetrical septal hypertrophy. No correlations between these echocardiographic findings and age of patients, severity of "biochemical" alterations and duration of the thyroid disease was observed.

Hardisty CA, Naik DR, Munro DS. Et al[22] studied thirty-nine patients with untreated hypothyroidism using echocardiography for the presence of a pericardial effusion. Effusions were present in twelve patients who tended to be more severely hypothyroid. Plasma creatine phosphokinase and lactate dehydrogenase levels were higher in the presence of an effusion.The concentration in the serum of such enzymes as creatine kinase, glutamic – oxaloacetic transaminase and lactate dehdrogenase may be increased.

The large heart, together with the haemodynamic and ECG alteration and the serum enzyme changes has been termed *Myxedema heart.*

Gonzales, Castillo et al[9] in a study on 'Cardiac manifestations of primary hypothyroidism' aimed to assess the effects of hypothyroidism on cardiac performance and structure. 19 patients with overt and 23 patients with subclinical hypothyroidism and 21 control subjects were studied by echocardiography.Patients were restudied one year after L-thyroxine therapy. Systolic function was assessed by the observed/predicted fractional shortening ratio. The predicted fractional shortening was calculated from the inverse relation of fractional shortening to end-systolic stress ($p < 0.0001$) in normal subjects. The observed/predicted fractional shortening ratio was lower ($p = 0.043$)

and left ventricular mass was higher (p = 0.028) in overt hypothyroidism than in subclinical hypothyroidism and control subjects. By multivariate analysis, fractional shortening ratio was related to thyroxine levels (p = 0.0002), systemic vascular resistance (p = 0.0001) and age (p = 0.0009), and left ventricular mass was related to thyroxine levels (p = 0.0004) and weight (p = 0.0001). Pericardial effusion was observed in 37% of patients with overt hypothyroidism and 9% of patients with subclinical hypothyroidism (p = 0.03), and was mainly related to TSH levels (p = 0.0098). Hormone replacement therapy increased systolic function in overt hypothyroidism. Left ventricular mass did not change after therapy. Pericardial effusion disappeared in all patients. It was concluded that primary hypothyroidism produces a decrease in myocardial contractility and an increase in left ventricular mass, both related to the severity of hormone deficiency. Pericardial effusion was mainly related to thyrotrophin plasma levels. Most of cardiac manifestations of hypothyroidism reversed with L-thyroxine therapy.

Landenson PW et al[10] in a study on ‘Recognition and management of cardiovascular diseases related to thyroid dysfunction’ published in American Journal of Medicine concluded that the

spectrum included pericardial effusion, heart failure and ischemic heart disease.

Gunderson et al[11]'s study on 'Hypothyroid cardiomyopathy an underdiagnosed cause of cardiac failure' published in American Journal Of Medicine found that patients with hypothyroid cardiomyopathy showed the presence of pericardial effusion in 75% of the patients.

The pericardial effusion in hypothyroidism accumulates so slowly that pericardium always has time to stretch. So patients are often asymptomatic.

Parving HH, Hansen JM, Nielson SL et al[25] studied ' Mechanisms of edema formation in myxedema' which was published in New England Journal of Medicine .Studies with radioactive albumin indicate that in Myxedema there is increased capillary permeability for protein which results in protein leakage, taken with retarded lymphatic drainage and the tendency to sodium and water retention in Myxedema, there results a combination of likely pathogenetic factors.

The fluid is usually clear with a specific gravity more consistent with exudates than transudation. The protein and cholesterol content

are usually elevated. But inflammatory cells or RBC are usually absent.

The lowest of all ECG voltages is seen with myxedema effusion and is probably additionally related to the frequent accompanying myocardial involvement, as are the non-specific T wave changes and bradycardia[26].

Cardiac tamponade as a complication of hypothyroidism is very rare; Jiménez-Nácher et al [12] cite that until 1992 less than 30 cases had been described in the world literature. This low incidence is probably due to the slow accumulation of fluid and to cardiac distensibility. Factors described as provoking cardiac tamponade include infection, spontaneous pericardial hemorrhage, thyroid therapy, and abdominal paracentesis. Identification of cardiac tamponade in hypothyroidism is therefore difficult and commonly mistaken for cardiac failure due to its symptoms of tachycardia, rise in venous pressure, lower limb edema, and increased cardiac silhouette on radiography.

The occurrence of paradoxical tachycardia maybe a clue to the impending tampanode.

In a study by Kabadi et al , the incidence of pericardial effusion in hypothyroidism was found to be 3-6%.[17]**.** Pericardial effusion is

reported to occur in 30% to 80% of subjects with hypothyroidism. However, these earlier studies were conducted when the diagnosis of hypothyroidism was only suspected and was confirmed only in the presence of classic clinical features. In contrast, the diagnosis has recently been established in the early mild stage or more often in an asymptomatic stage because of more frequent or routine determinations of thyroid function tests, especially in the elderly. Thus the subjects in the older studies were severely hypothyroid at the time of diagnosis and may not be representative of the present hypothyroid population. For this reason, 30 subjects with hypothyroidism were evaluated with echocardiography to reassess the evidence of pericardial effusion in this disorder. Only two subjects demonstrated pericardial effusion, and in only one of them with severe disease could the pericardial effusion be attributed to hypothyroidism, since it resolved on the patient's attaining the euthyroid state. Thus the incidence of pericardial effusion was only 3% to 6%, depending on the inclusion of one or both subjects, an extremely infrequent occurrence when compared with that of previous studies. Moreover, the occurrence of pericardial effusion in hypothyroidism appears to be dependent on the severity of the disease. Thus pericardial effusion may be a frequent manifestation in myxedema, an advanced severe stage, as previously found, but a rare association of hypothyroidism, an early

mild stage, because of the timeliness with which the latter condition is nowadays detected.

Hypothyroidism is associated with clinically significant cardiovascular involvement. In hypothyroidism, the cardiovascular derangements include pericardial effusion, congestive heart failure, hypertension, hyperlipidaemia, coronary artery disease, and primary pulmonary hypertension.

Various studies show differing prevalence of pericardial effusion among patients with hypothyroidism. The current study has been undertaken to estimate the prevalence of pericardial effusion in hypothyroidism and to correlate it with severity of hypothyroidism.

CAUSES OF HYPOTHYROIDISM

1. Thyroid -95%
    A. Thyroprivic
        i. Congenital or development defects.
        ii. Primary idiopathic
        iii. Post ablative (Radio-iodine, surgery)
        iv. Post radiation (Lymphoma)
    B. Goitrous:
        i. Heritable biosynthetic defects.
        ii. Maternally transmitted (Iodides, anti thyroid agents)
        iii. Iodine deficiency
        iv. Drug induced (PAS, iodides, Phenyl butazone, antipyrin, lithium)
        v. Chronic thyroiditis –(Hashimoto's, Riedel's and de Quervain's)
2. Suprathyroid (Trophoprivic) – 5%
3. Self limited
    A. Following withdrawal of suppressive thyroid therapy
    B. Sub acute thyroiditis and chronic thyroiditis with transient hypothyroidism.

Symptoms of hypothryoidism:

- Fatigue, loss of energy, lethargy
- Weight gain
- Decreased appetite
- Cold intolerance
- Dry skin
- Hair loss
- Sleepiness
- Muscle pain, joint pain, weakness in the extremities
- Depression
- Emotional lability, mental impairment
- Forgetfulness, impaired memory, inability to concentrate
- Constipation
- Menstrual disturbances, impaired fertility
- Decreased perspiration
- Paresthesia and nerve entrapment syndromes
- Blurred vision
- Decreased hearing
- Fullness in the throat, hoarseness

Physical signs of hypothyroidism

Signs found in hypothyroidism are usually subtle and require a careful physical examination. Often, many signs are dismissed as part of aging; however, consider a diagnosis of hypothyroidism when such signs are present. Physical signs of hypothyroidism include the following:

- Hypothermia
- Weight gain
- Slowed speech and movements
- Dry skin
- Jaundice
- Pallor
- Coarse, brittle, strawlike hair
- Loss of scalp hair, axillary hair, pubic hair, or a combination
- Dull facial expression
- Coarse facial features
- Periorbital puffiness
- Macroglossia,
- Goiter
- Hoarseness

- Decreased systolic blood pressure and increased diastolic blood pressure
- Bradycardia
- Pericardial effusion
- Abdominal distension, ascites (uncommon).
- Nonpitting edema (myxedema)
- Pitting edema of lower extremities
- Hyporeflexia with delayed relaxation, ataxia, or both

Additional signs specific to different causes of hypothyroidism, such as diffuse or nodular goiter or pituitary tumor, can occur.

PERICARDIAL EFFUSION – CAUSES

a) Infectious: viral, bacterial, tuberculosis, mycotic

b) Non-infectious – myocardial infarction, uraemia, neoplasia, myxedema, cholesterol, chylopericardium, trauma, irradiation, idiopathic.

c) Hypersensitivity or autoimmunity: rheumatic fever, post cardiac injury.

MATERIALS AND METHODS

- **Setting** – Out Patient Department, Department of Endocrinology, Government General Hospital, Madras Medical College, Chennai.
- **Collaboration Departments**- Department of Endocrinology, GGH, Chennai.
- **Ethical committee Approval**- Obtained
- **Design of study**- Descriptive Study
- **Period of study**- February 2006- June 2007
- **Sample size**- 70 patients

SUBJECTS

Inclusion criterita

1. Newly diagnosed patients with elevated TSH and decreased T3 and T4 .
2. Age of the patients more than 18 years.

Exclusion criteria

1. Patients already on treatment with Thyroxine.
2. Patients with other known causes of pericardial effusion – tuberculosis, uremia malignancy, irradiation, connective tissue

disorders, acute febrile onset, trauma, myocardial – infraction, cardiac surgery.

The reference values for the following parameters have been adopted from Harrison's Principles of Internal Medicine[14].

Serum hormone concentration

Sensitive and specific methods for the determination of free and total concentration of blood are now available. These methods are the radio- immunoassay, florescent immunoassay and the enzyme linked immunoassay.

The reference values for these tests have been adopted from the standard values given in Harrison's textbook of Internal Medicine 17th edition.

Serum Total T4 concentration:[14]

The normal range of total T4 concentration in healthy adults is between 4.5-10.9 µg/dl with variation in normal range between laboratories. **Serum Total T3 concentration:[14]**

The normal range of total T3 concentration in healthy adults in 60-181 ng/dl with the variation between different laboratories.

Serum thyroid stimulating hormone (TSH) concentration:[14]

The normal range of TSH concentrations in adults vary between 0.5 -4.7^{0} µunits/ml. This is measured by the radio – immunoassay method. It is an extremely useful measurement in the diagnosis and management of hypothyroidism.

Other lab investigations:[14]

1. *Haemoglobi*n – Determined by the haemoglobinometer

   Normal range

   Men – 13.5 – 17.5gm%

   Women – 12.0 – 16.0 gm%

2. *Differential count of white blood cells:*

Differential counts	**Normal range (%)**
Neutrophils	40-70
Lymphocytes	22-44
Monocytes	4-11
Eosinophils	0-8
Basophils	0-3

3. *ESR* was measured by the Westegren method

   Normal range 0-20mm in 1 hour.

1. CHEST RADIOGRAPH:

   - Look for cardiomegaly

2. ELECTROCARDIOGRAPH

   - Look for Bradycadria ; low voltage complexes, T wave changes, heart block

3. ECHOCARDIOGRAPHY:

   - Look for Pericardial effusion, systolic/diastolic dysfunction, Asymmetrical septal hypertrophy.

Data collection

Patients attending the out patient Clinic of the Department of Endocrinology who satisfied the inclusion criteria were registered for the study after obtaining their consent.

A detail questionnaire was used to elicit symptoms of hypothyroidism. The patient was examined to look for signs of hypothyroidism.

Special attention was given to examination of the cardiovascular system to look for clinical features of pericardial effusion.

Blood was drawn for Complete hemogram, lipid profile and thyroid profile and sent to the Biochemistry Laboratory.

An ECG, Chest X ray and an Echocardiogram were obtained for all the patients.

The data was statistically analysed using SPSS 2007 software.

OBSERVATIONS AND RESULTS

The prevalence of pericardial effusion in this study was **17%.** 12 out of the 70 hypothyroid patients showed evidence of pericardial effusion.

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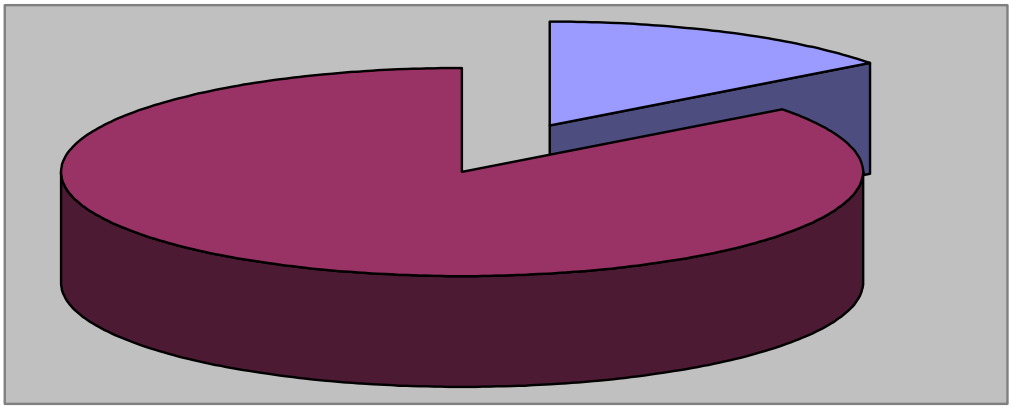
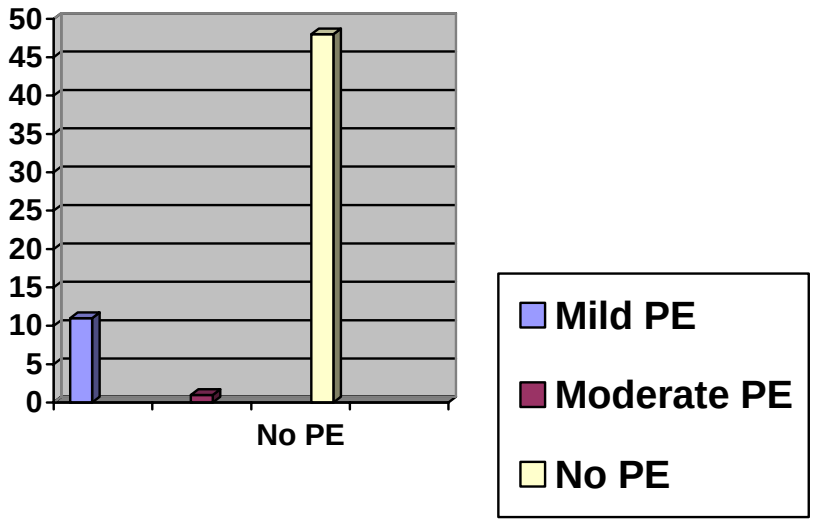


Mild pericardial effusion was found in 11 patients (15.71%) and moderate pericardial effusion in 1 patient (0.01%).

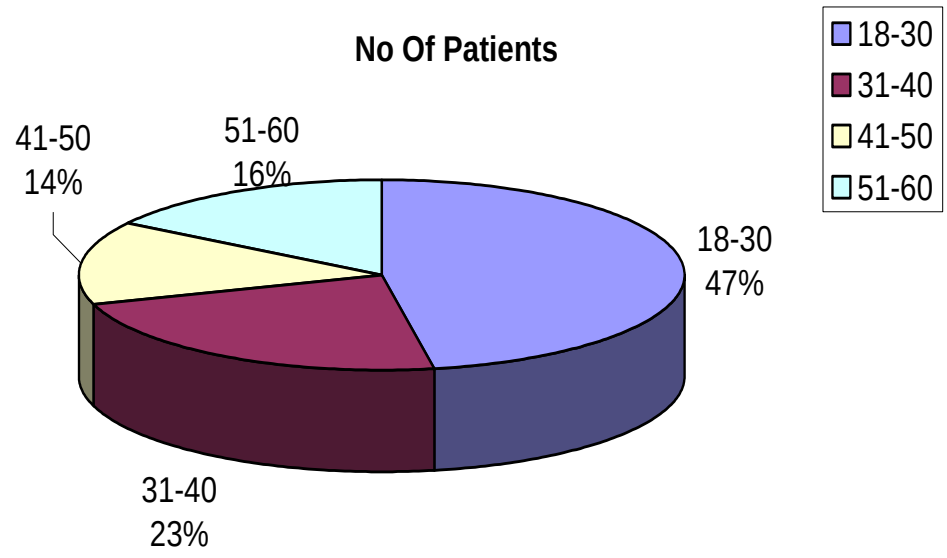


Percardial effusion was noted in 17 % of patients by 2D echo. It was always mild (on average anteriorly 0.5 cm and posteriorly 0.4 cm) to moderate (anteriorly 0.7 cm and posteriorly 1.9 cm). Mild effusion was present in 90 % of patients. Moderate effusion was present in only one patient. Severe pericardial effusion or cardiac Tamponade was never observed. Left ventricular dysfunction in the form of global hypokinesia & reduced ejection fraction was present in one patient. In another patient mild pericardial effusion was associated with mild septal hypertrophy and mild global hyperkinesia leading to mild left ventricular dysfunction. None of these patients had evidence of pericardial thickening.

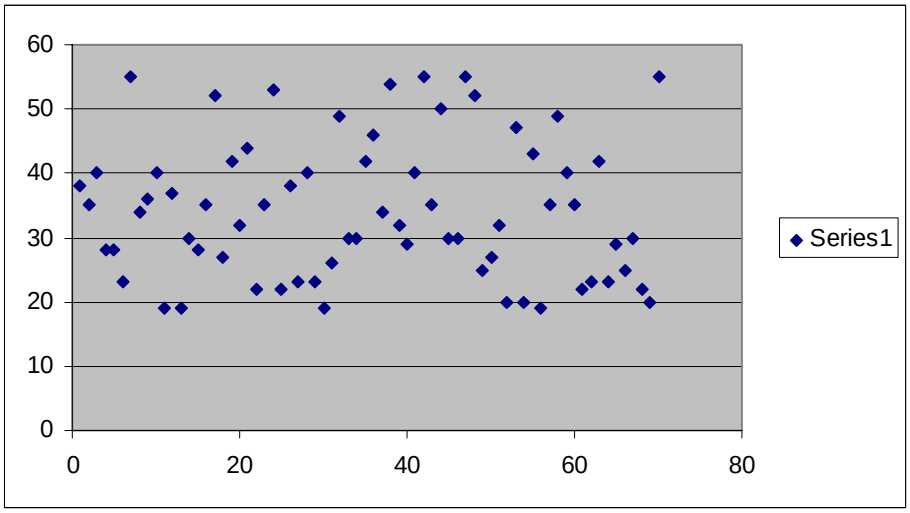
Age:

The age distribution of the patients ranged between 18yrs and 60 yrs with a mean age of 33.97 yrs. The age distribution in the study group was as follows-

AGE GROUP(yrs)	NO. OF PATIENTS	PERCENTAGE OF PATIENTS(%)
18-30	33	47
31-40	16	23
41-50	10	14
51-60	11	16



The following scatter diagram shows the age distribution in the study group.



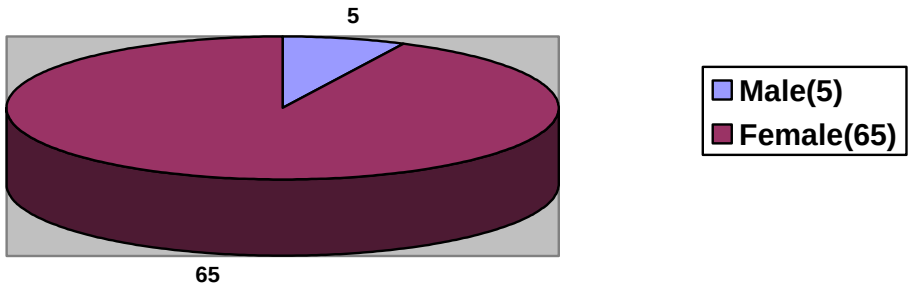
The average age of those with PE is 34.42yrs and that for those without PE is 34.24 yrs. No statistical significance was observed between age of the patient and occurrence of Pericardial Effusion.

	Age(yrs)	**CI**	**P value**
PE	34.42	±5.07	0.95
No PE	34.24	±2.49	

SEX:

Of the 70 hypothyroid patients 65 were female and 5 were male.

M:F ratio was found to be 1:13.



Among the males one patient (20%) developed PE while among the females 11 patients (16.92%) developed PE.

	PE	No PE	P Value
Males	1	4	0.87
Females	11	54	

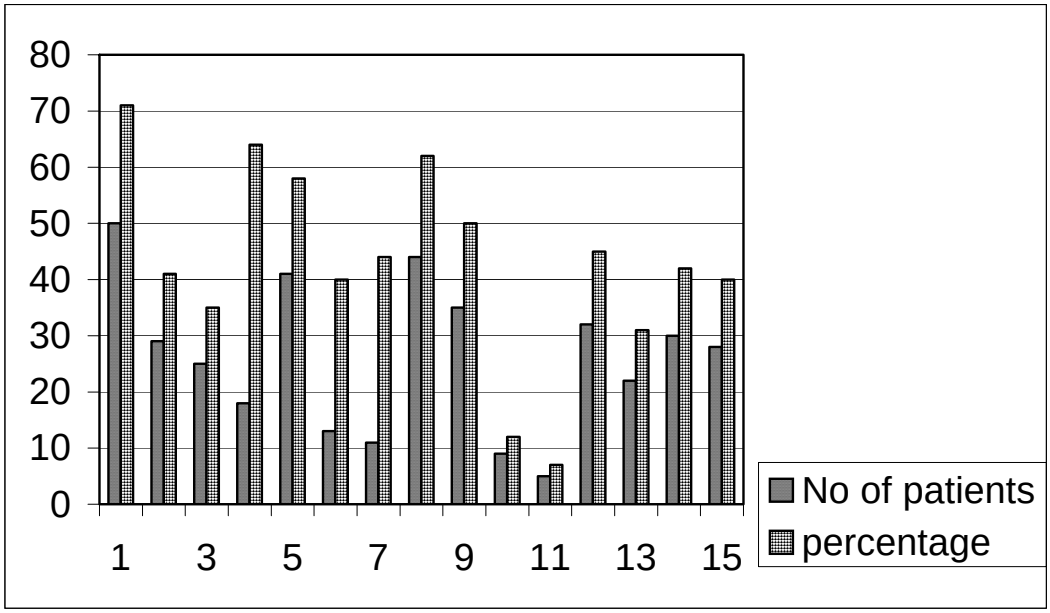
No statistical significant association was found between gender of the patient and pericardial effusion (P 0.87)

Symptoms

Lethargy and weight gain were the most common symptoms, which were present in 71% and 64 % of the patients respectively. Dry skin and peri-orbital swelling were observed in 60 % of the patients. 12 % had dyspnea and 44% had hoarness of voice. 42% complained of memory impairment, constipation and anorexia, cold in tolerance and distal parasthesias. Chest pain was present 7 % of patients, menstrual disturbances in the form of menorrhagia were observed in 42 %.

Symptoms of hypothyroidism were distributed among the study group as follows.

S.NO	Symptom	No. Of patients	Percentage Of Patients
1	Lethargy	50	71
2	Aches And Pains	29	41
3	Hair Loss	25	35
4	Weight Gain	45	64
5	Dry Skin	41	58
6	Cold Intolerance	28	40
7	Hoarseness Of Voice	31	44
8	Swelling Around Eyes And Limbs	44	62
9	Anorexia	35	50
10	Dyspnea	9	12
11	Chest Pain	5	7
12	Constipation	32	45
13	Menstrual Disturbances	22	31
14	Memory Impairment	30	42
15	Tingling In Toes And Fingers	28	40



Only two of the 12 patients with pericardial effusion had cardiovascular symptoms like chest pain and breathlessness. 11 patients without PE still did complain of chest pain and/or dyspnea . On statistically analyzing we see that cardiovascular symptoms not significantly associated with pericardial effusion (P<0.001).

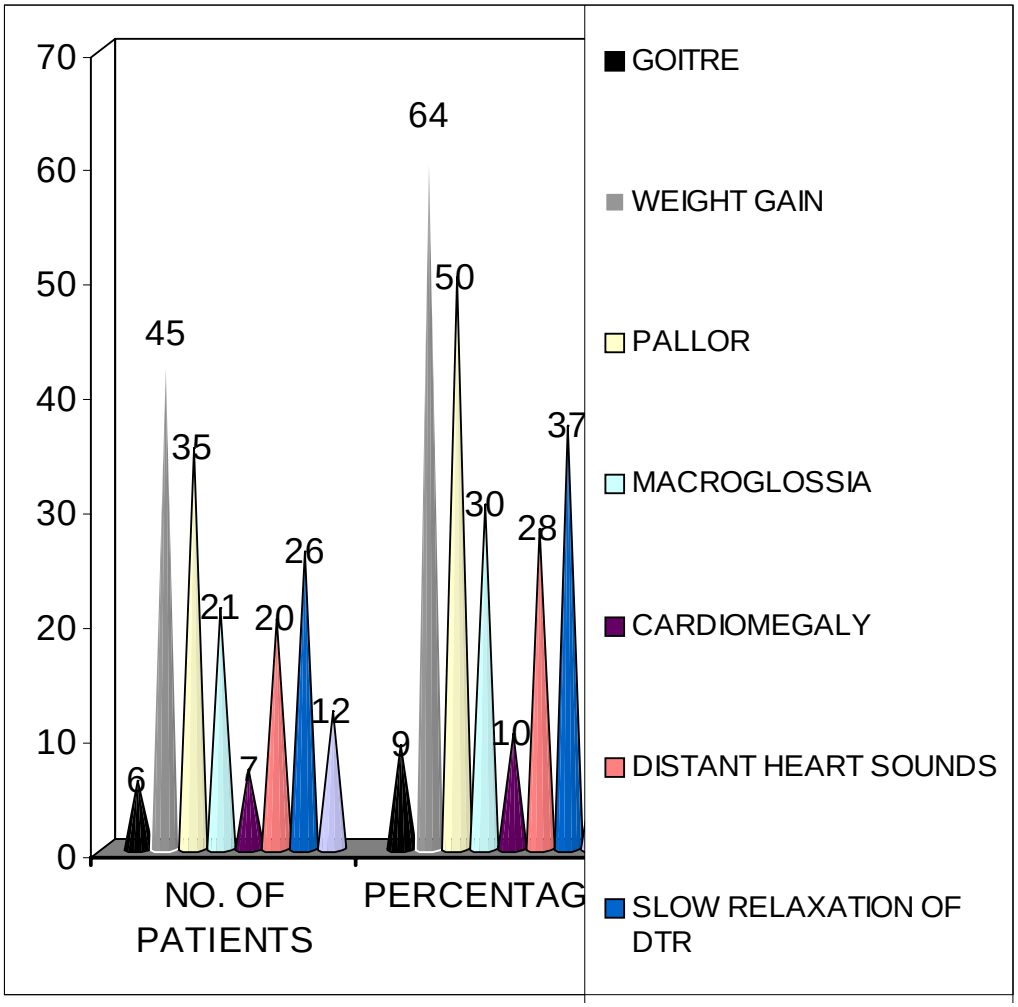
	Symptomatic	**Asymptomatic**	**P value**
PE	2	10	<0.001
No PE	11	37	

Signs

Over weight was a common finding on clinical examination, which was present in 64 % of patients. The mean pulse rate was 80 / min and mean blood pressure 110 / 70 mm of Hg. Pallor was present in 50 % of patients. Clinically indistinct heart sounds and cardiomegaly were present 28 % and 10 % of patients respectively. Delayed deep tendon reflex were noticed in 37 % patients. Macroglossia was observed in 30 % of patients. None of these patients had pulses paradoxus or features suggestive of cardiac failure.

The signs of hypothyroism elicited in the study group were as follows :

S.NO	Sign	No. Of patients	Percentage
1	Goitre	6	9
2	Weight Gain	45	64
3	Pallor	35	50
4	Macroglossia	21	30
5	Cardiomegaly	7	10
6	Distant Heart Sounds	20	28
7	Slow Relaxation Of DTR	26	37
8	Galactorrhoea	12	8



Clinical signs of PE like distant heart sounds and/or cardiomegaly on percussion were found in 3 patients among those with PE as documented on echo. But these signs were also found in 16 among the patients without PE.

	Signs present	**Signs absent**	**P value**
PE	3	9	<0.001
No PE	16	32	

On statistically analyzing the data we find that there is a significant association between presence of signs of effusion and its documentation on echo.

Macroglossia:

This clinical feature was found in 21 patients of hypothyroidism. 5 of these patients developed pericardial effusion (23.8%), while among the 49 patients without macroglossia pericardial effusion was found in 7 patients (14.28%).

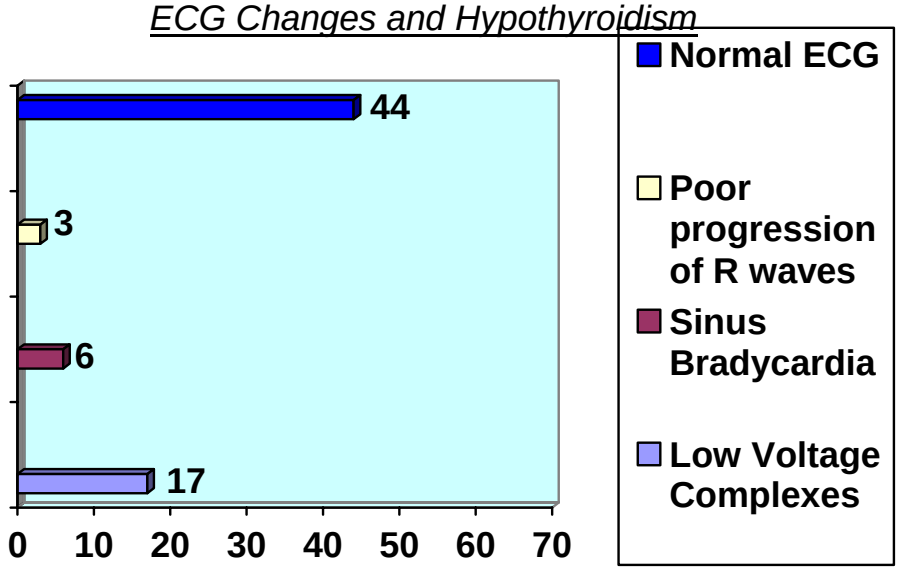
On statistically analyzing the data we find that there is a significant association between presence of macroglossia and pericardial effusion. (P<0.001)

	Macroglossia	**No Macroglossia**	**P value**
PE	5	7	<0.001
No PE	17	42	

ECG findings

Low voltage complexes were found in 17 patients (24.29%), sinus bradycardia was found in 6 patients (0.09%), poor progression of R waves in 3 patients (0.04%). The remaining 44 patients had a normal ECG.

ECG Changes and Hypothyroidism

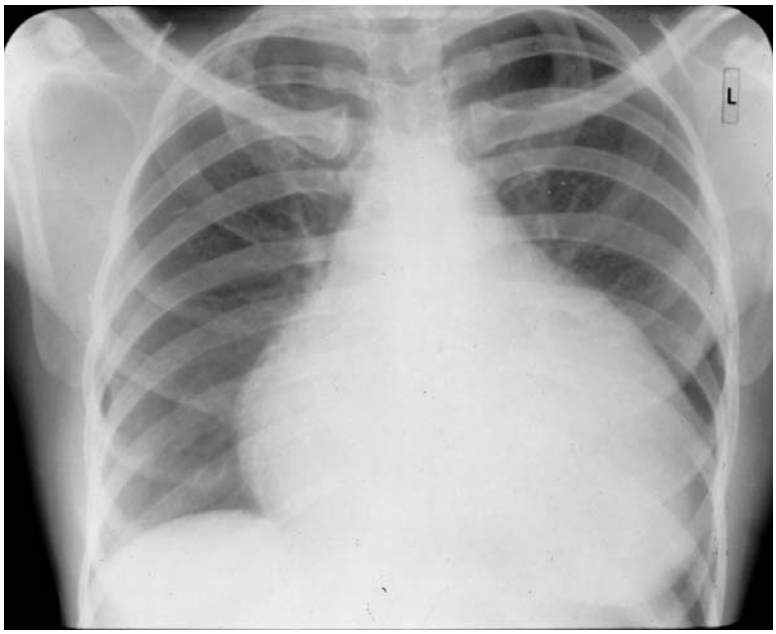


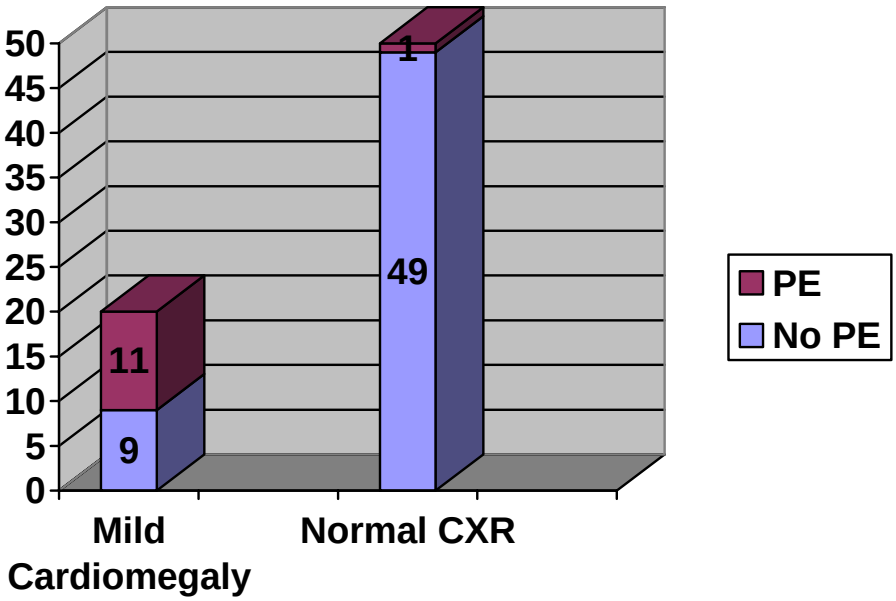
Among the 26 patients with ECG changes echo showed pericardial effusion in 12 patients (46.15 %). While none of the 44 patients with Normal ECG showed pericardial effusion. So ECG can be used as a screening tool to predict Pericardial effusion.

Among the patients with Pericardial effusion ECG changes were found in all 100%.

Chest X ray

Chest films showed Mild cardiomegaly in 20 patients (28.57%). 11 of these 20 patients had pericardial effusion on echocardiography. One patient with echo proven pericardial effusion had normal chest X ray. So chest X rays can be used to look for clues for pericardial effusion.





Serum Thyroid hormones and Pericardial effusion:

The mean serum TSH, T3 and T4 were compared between patients with pericardial effusion and those without.

It was seen that mean serum TSH was statistically higher in patients who were found to have pericardial effusion than in the control group

A similar association was also found between low mean serum T4 and Pericardial Effusion but no association was documented between low mean serum T3 and presence of pericardial effusion..

	Mean TSH	**CI**	**P value**
PE	41.22	±14.21	0.005
No PE	28.26	±5.24	

	Mean T3	**CI**	**P value**
PE	88.69	±20.79	0.643
No PE	92.74	±7.50	

	Mean T4	**CI**	**P value**
PE	4.08	±0.91	0.005
No PE	6.04	±0.57	

DISCUSSION

Prevalence of pericardial effusion

Hypothyroidism, a disease with a multisystem involvement that may present clinically in various forms, one being unusual pericardial effusion, a cardiovascular complication. Early studies of overtly hypothyroid patients suggested that pericardial effusion was a relatively common phenomenon.[15, 16] . More recent echocardiographic studies of the hypothyroid population show a widely varying incidence of pericardial effusion from 3 to 88 %.

In our study 17% of the hypothyroid patients were found to have pericardial effusion on Echocardiography.

Mancuso L, Lo Bartolo G, Iacona MA et al studied 25 patients with primary hypothyroidism using M-Mode and 2 D Echo and reported the incidence of pericardial effusion to be 88%.[8]

According to KABADI U.M. & KUMAR S.P. et al[17] the incidence of pericardial effusion was 30 – 80 % in full blown of hypothyroids. However, these earlier studies were conducted when the diagnosis of hypothyroidism was only suspected and was confirmed only in the presence of classic clinical features. In contrast, the

diagnosis has recently been established in the early mild stage or more often in an asymptomatic stage because of more frequent or routine determinations of thyroid function tests, especially in the elderly. Thus the subjects in the older studies were severely hypothyroid at the time of diagnosis and may not be representative of the present hypothyroid population. Due to earlier detection, the incidence has now fallen to 3% – 6%[117]

Gunderson et al[11] studied 20 patients with hypothyroid cardiamyopathy. Pericardial effusion was demonstrated in 15 of the patients which disappeared with thyroxin therapy..

Age

The mean age of the patients studied was 33.97 yrs and most of the patients were found between the age group of 18 and 44 years.

Literature review showed that the mean age at diagnosis of auto immune thyroiditis is 60 years[1] and the prevalence of hypothyroidism is said to increase with age.

But this pattern was not observed in our study group , probably due the relatively small number of cases studied.

On analyzing the mean age between patients with pericardial effusion and those without, no significant difference was found. So it has been concluded that age of the patient does not play a role in incidence of pericardial effusion.

Sex

The male: female ratio in this study has been found to be 1:13.

Community studies use slightly different criteria for determining hypothyroidism; therefore, female-to-male ratios vary. Generally, thyroid disease is much more common in females than in males, with reports of prevalence 2-8 times higher in females.[5]

We compared the prevalence of pericardial effusion among male and female hypothyroids and we found that there was no significant association between sex of the patient and incidence of pericardial effusion.

Symptoms and signs

Available description of hypothyroid associated pericardial effusion suggest that patients present far more commonly with signs and symptoms of the underlying endocrine disorder than with the sequelae of pericardial effusion.[18]

In this study 71% of the patients complained of generalized myalgia and lethargy. Other symptoms of hypothyroidism were found less commonly. But symptoms suggesting involvement of cardiovascular system like dyspnea on exertion and chest pain were found in only 14% of the patients.

Similarly signs of pericardial effusion like muffled heart sounds and cardiomegaly were found only in 28% while signs of hypothyroidism like weight gain and pedal edema was found in around 64% of the patients.

When analysed statistically we did find a significant association between presence of signs/symptoms and occurrence of pericardial effusion.

Macroglossia

In this study group macroglossia was found in around 30% of the patients. Macroglossia has been described as a clinical feature of hypothyroidism and it has been proposed that it is caused by the accumulation of fluid in the tongue[19].

Nicola Meares, Stanky Braude. M.et al described a case of ‘Massive macroglossia as a presenting feature of hypothyroid-

associated pericardial effusion'. In this case, drainage of pericardial effusion resulted in prompt resolution of macroglossia. They argued that the macroglossia could have been a direct consequence of the effusion which could have led to venous engorgement.[20]

Among the 21 patients with macroglossia five patients had pericardial effusion and on statistically comparing it with patients without macroglossia it was found that this sign was more commonly present in patients with pericardial effusion.

ECG and Chest X ray

In patients with pericardial effusion the expected ECG changes are – low voltage complexes and poor progression of R waves. Chest x ray can help in diagnosing pericardial effusion by revealing cardiomegaly. In this study we analysed the prevalence of pericardial effusion in those with ECG and Chest X ray changes suggestive of its existence.

There was found to be a significant correlation between ECG changes and pericardial effusion. Sinus bradycardia was found more commonly in patients with severe hypothyroidism. Chest X ray was also found to reliably predict the presence of underlying PE.

So these simple bedside clinical investigative tools can be used to predict underlying pericardial effusion in patients with hypothyroidism.

Tajiri J, Morita M, Higashi K et al[21] in order to clarify the cause of low voltage QRS complex seen on ECG (low voltage) studied thyroid hormones, LDH isozyme and pericardial effusion (PE) in 39 patients with primary hypothyroidism. it was suggested that in hypothyroidism low voltage was brought about by a combination of both severe thyroid hormone deficiency and large PE. In addition, elderly patients over 60 years had low voltage more frequently than did patients under 59 years.

But no specific electrocardiographic changes associated with the presence of an effusion could be associated with a normal cardiac silhouette on a standard P.A. chest X-ray in a study of hypothyroid patients done by Hardisty CA, Naik DR, Munro DS et al[22]

Severity of disease and Pericardial effusion

Pericardial effusion was reported in early studies in 30 -80% of subjects with hypothyroidism. However, these earlier studies were conducted when the diagnosis of hypothyroidism was made by classic clinical features. In contrast, the diagnosis has recently been

established in the early mild stage or in an asymptomatic stage because of the frequent use of highly sensitive thyroid function tests. Moreover, the occurrence of pericardial effusion in hypothyroidism appears to be dependent on the severity of the disease. Thus, a large pericardial effusion may be a frequent manifestation in myxoedema, but a rare association of hypothyroidism in early mild stage.[23]

But in studies done by Kabadi et al[17] and Yamamato[24] et al it has been demonstrated that no correlation exists between duration or severity of hypothyroidism and incidence of pericardial effusion.

In our study we compared mean Serum T3, Serum T4 and Serum TSH levels between the patients with pericardial effusion and those without effusion. Mean TSH in patients with Pericardial effusion was 41.22 while that of patients without it was 28.26. Mean serum T4 in patients with pericardial effusion was 4.08 and mean serum T4 in the control group was 6.04. It was seen that high serum TSH and low Serum T4 were statistically associated with occurrence of Pericardial effusion($p=0.005$). So we conclude that pericardial effusion is more commonly found in patients with severe hypothyroidism.

SUMMARY

- 70 patients were included in this study
- 65 cases were female, 5 cases were male.
- Male female ratio has been found to be 1:13
- Most of the patients were found in the age group of 18 to 44 years.
- 17% of the patients had pericardial effusion on echocardiography
- 71% of patients complained of fatigue and malaise
- Cardiovascular symptoms like dyspnea and chest pain were found in 14% of the patients and signs of pericardial effusion were found in 28% of the patients.
- Macroglossia was found in 30% of the patients
- Pericardial effusion was found more often in patients with more severe hypothyroidism when T3, T4 and TSH were used as tools to assess severity.

CONCLUSION

- The prevalence of pericardial effusion among newly detected hypothyroid patients was 17%
- Age and sex of the patient were not found to be risk factors for the development of pericardial effusion among patients with hypothyroidism.
- Clinical features of pericardial effusion show statistically significant association with its presence on echocardiogram.
- Macroglossia was more commomly found in patients with Pericardial effusion
- ECG and CXR can be used to predict the presence of Pericardial effusion.
- When serum thyroid hormone levels are used as a marker of severity, pericardial effusion is found more commonly in patients with more severe disease.

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PROFORMA

Name Age Sex

Complaints Marital Status:

Occupation

Address

Date

History of present illness

SYPTOMATIC ENQUIRY:

Weight gain

Cold intolerance

Hoarseness of voice

Dyspnea

Chest pain

Swelling around the eyes, hand and feet

Night blindness

Fatigability

Somnolence

Constipation

Anorexia

Tinnitus

Deafness

Visual disturbance

Muscle weakness

Aches and pains

Libido

Potency

Menstrual disturbance

Headaches

Vomiting

Secretion from nipple

Hair loss

History of Tingling and numbness

Family history

Past history

History of radiation to neck

Neck surgery

General and physical examination

Appearance

Height

Weight

Pallor

Icterus

Lymphadenopathy

Pulse rate

Blood pressure

Peripheral pulsation

Edema feet

Exophthalmos

Peri-orbital edema

Goiter

Skin/ Nail – soft, scaly ; war/cold; moist/dry; onycholysis

Breasts – Galactorrohea

Hair – Coarse; loss of hair on scalp, eyebrow, axillary, pubic;

CVS - heart rate (Paradoxical pulse), heart sounds, murmurs cardiomegaly, evidence of Pericardial Effusion.

Respiratory system

Abdomen

CNS – Gait, DTR, cerebellar signs, muscle wasting, muscle hypertrophy, peripheral nerves.

Fundus

Clinical Diagnosis

Treatment

Follow-up

INVESTIGATIONS:

1. Haemoglobin – Determined by the haemoglobin meter

   Normal range

   Men – 13 – 17gm%

   Women – 11.5 – 16.5 gm%

2. Differential count of white blood cells:

Differential counts	Normal range (%)
Neutrophils	40-75
Lymphocytes	20-45
Monocytes	2-10
Eosinophils	1-6
Basophils	0-1

3. ESR was measured by the Westegren method

   Normal range 0-20mm in 1 hour.

4. Lipid profile was done by auto analyzer.

	Normal range
Ser total cholesterol	150 – 240 mg/dl
Ser HDL cholesterol	45 -65 mg/dl
Ser triglycerides	100-190 mg/dl
Ser LDL cholesterol	66-718 mg/dl

5. Radio –immunoassay method:

Serum T3	70-200 ng/dl
Serum T4	5-12 µg/dl
Serum TSH	0.5 -5 µU/ml

6. CHEST RADIOGRAPH:
7. ELECTROCARDIOGRAPH
    - Bradycadria ; low voltage complexes, T wave changes, heart block
8. ECHOCARDIOGRAPHY:
    - Pericardial effusion, systolic/diastolic dysfunction

    Asymmetrical septal hypertrophy.

MASTER CHART

CASE NO	AGE	SEX	T3 ng/dl	T4 µg /dl	TSH mIu/ml	ECG	CXR	2D ECHO
1	19	F	112.9	7.5	11.59	Normal	Normal	No PE
2	55	F	65	2.8	25.50	Low voltage complexes	Mild cardiomegaly	Mild PE Ant 0.8cm Post 0.5cm
3	30	F	129.85	9.11	10.90	Normal	Normal	No PE
4	19	F	18.08	3.11	23	Low voltage complexes. poor progression of R waves	Mild cardiomegaly	Mild to moderate PE Ant 0.7cm Post 1.2cm
5	28	F	98	5.2	9.32	Low voltage complexes	Normal	No PE
6	35	F	142	5.2	11.39	Normal	Normal	No PE
7	52	F	98	11.42	10.56	Normal	Normal	No PE
8	27	M	59.8	7.55	12.4	Normal	Normal	No PE
9	42	F	145	3.79	13.9	poor progression of R waves V1-V4	Mild cardiomegaly	No PE
10	32	F	132	5.3	13.5	Normal	Normal	No PE
11	44	F	123	5.4	10.8	Low voltage complexes	Mild cardiomegaly	No PE
12	22	F	84.80	5.15	9.4	Normal	Normal	No PE
13	35	F	94.88	5.88	8.6	Normal	Normal	No PE
14	28	F	112.50	6.33	33.08	Sinus bradycardia	Mild cardiomegaly	Mild PE Ant 0.7cm Post 0.3cm

CASE NO	AGE	SEX	T3 ng/dl	T4 µg /dl	TSH mIu/ml	ECG	CXR	2D ECHO
15	53	F	109	8.2	10.4	Low voltage complexes	Normal	No PE
16	22	F	84	5.4	9.8	Normal	Normal	No PE
17	38	F	113.5	4.25	10.4	Sinus bradycardia	Mild cardiomegaly	No PE
18	23	F	103.62	5.24	9.28	Normal	Normal	No PE
19	40	F	117	7.8	8.2	Low voltage complexes	Mild cardiomegaly	No PE
20	23	F	145	3.79	9.8	Normal	Normal	No PE
21	19	F	89	9.1	10.9	Normal	Normal	No PE
22	26	F	85.2	6.11	13.9	Normal	Normal	No PE
23	49	M	122	4.24	11.2	Low voltage complexes with prolongation of PR interval	Mild cardiomegaly	No PE
24	30	F	82	5.2	9.2	Normal	Normal	No PE
25	30	F	96.5	4.2	12.12	Normal	Normal	No PE
26	28	F	117	2.25	52.9	Low voltage complexes with sinus bradycardia	Mild cardiomegaly	Mild PE Ant 0.7cm Post 0.3cm
27	42	F	95.9	4.7	10	Normal	Normal	No PE
28	46	F	85	8.7	11.2	Normal	Normal	No PE
29	34	F	82.5	6.11	9.2	Normal	Normal	No PE
30	54	M	142	3.53	10.12	Low voltage complexes	Mild cardiomegaly	No PE
31	32	F	85.4	9.14	12.9	Normal	Normal	No PE
32	29	F	92.5	8.6	11	Normal	Normal	No PE
33	40	F	156	5.2	13.8	Normal	Normal	No PE

CASE NO	AGE	SEX	T3 ng/dl	T4 µg /dl	TSH mIu/ml	ECG	CXR	2D ECHO
34	55	F	125.8	9.5	12.35	Normal	Normal	No PE
35	35	F	93.4	4.5	10.2	Normal	Normal	No PE
36	37	F	65.5	3.8	52.5	Low voltage complexes	Mild cardiomegaly	Moderate PE Ant 0.7cm Post 1.9cm
37	50	F	72	5.5	9.59	Normal	Normal	No PE
38	22	F	95.2	2.9	64.2	Sinus bradycardia	Mild cardiomegaly	Mild PE Ant 0.5cm Post 0.6cm
39	30	F	105.2	3.6	10.2	Normal	Normal	No PE
40	30	F	82.5	5.3	12.5	Normal	Normal	No PE
41	40	F	107.2	3.3	52.9	Sinus bradycardia	Mild cardiomegaly	Mild PE Ant 0.8cm Post 0.9cm
42	23	F	88	3.5	28.9	Poor progression of R waves	Mild cardiomegaly	Mild PE Ant 0.84cm Post 0.36cm
43	55	F	109.8	9.11	8.52	Low voltage complexes	Mild cardiomegaly	No PE
44	52	M	112.5	3.4	12.9	Low voltage complexes	Normal	No PE
45	25	F	92.5	7.9	8.2	Normal	Normal	No PE
46	27	F	110.8	5.2	11.5	Normal	Normal	No PE
47	32	F	109.2	6.5	12.2	Normal	Normal	No PE
48	20	F	88.5	4.5	12.5	Normal	Normal	No PE
49	47	F	119.2	4.92	11.5	Low voltage complexes	Normal	No PE
50	35	F	45.2	2.59	40.12	Sinus bradycardia	Mild cardiomegaly	Mild PE Ant 0.5cm Post 0.6cm
51	20	F	109.2	6.08	12.60	Normal	Normal	No PE
52	43	F	80.92	3.9	11.2	Low voltage complexes	Normal	No PE
53	19	F	93.45	4.92	10.92	Normal	Normal	No PE

CASE NO	AGE	SEX	T3 ng/dl	T4 µg /dl	TSH mIu/ml	ECG	CXR	2D ECHO
54	34	F	133	6.2	24.5	Poor progression of R waves	Mild cardiomegaly	Mild PE Ant 0.8cm Post 0.7cm
55	35	F	88.7	5.2	12.5	Normal	Normal	No PE
56	49	F	125.2	5.2	11.9	Normal	Normal	No PE
57	40	F	103.65	9.11	12.5	Normal	Normal	No PE
58	35	F	90.9	10.52	11.52	Normal	Normal	No PE
59	22	F	139.2	7.5	13.3	Normal	Normal	No PE
60	23	F	79.2	5.22	10.92	Normal	Normal	No PE
61	40	M	105.2	6.2	52.5	Low voltage complexes	Mild cardiomegaly	Mild PE Ant 0.5cm Post 0.6cm
62	42	F	80.9	4.9	11.2	Normal	Normal	No PE
63	23	F	142.2	7.9	9.2	Normal	Normal	No PE
64	29	F	98.2	6.7	8.9	Normal	Normal	No PE
65	25	F	89.2	3.52	10.3	Normal	Normal	No PE
66	30	F	88.9	7.52	12.2	Normal	Normal	No PE
67	22	F	95.2	9.04	9.2	Low voltage complexes	Mild cardiomegaly	No PE
68	20	F	80.2	3.56	12.4	Normal	Normal	No PE
69	36	F	64.5	2.50	34.5	Low voltage complexes	Normal	Mild PE Ant 0.8cm Post 0.7cm
70	55	F	123.2	4.5	9.09	Sinus bradycardia	Mild cardiomegaly	No PE