

ORIGINAL ARTICLE

Cardiovascular Manifestations in Newly Diagnosed Hyperthyroid Patients and their Outcome with Anti-Thyroid Treatment

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Abstract

Objectives: To evaluate the incidence of cardiovascular abnormalities in newly identified hyperthyroid patients and their outcome with anti-thyroid therapy.

Methods: A total of 96 patients who were newly diagnosed to have hyperthyroid disease were screened and out of them, 40 patients who presented with cardiovascular symptoms and sign were included in study (30 females, 10 males). Hyperthyroid patients were re-evaluated after antithyroid therapy. Findings in patients were compared at presentation, and after 3 month of treatment. All had undergone a structured cardiovascular history and examination, including measurements of blood pressure (BP) and pulse rate. All had resting 12-lead electrocardiogram and 2D ECHO.

Results: Cardiovascular symptoms and signs, as well as abnormal hemodynamic and dysrhythmias, especially supraventricular, were frequent among patients with hyperthyroidism. Palpitation and atrial fibrillation (AF) were more recurrent in overt hyperthyroid subjects than those with subclinical hyperthyroidism and remained more prevalent after 3 month of antithyroid treatment in that subject who had persistently high serum T3 and T4 level.

Conclusion: Cardiovascular abnormalities are one of the most common presentations in patients with hyperthyroidism and they respond very well to treatment before the structural changes occur in the cardiovascular system.

Introduction

Hyperthyroidism has been identified by cardiovascular phenomenon for more than two centuries and envisaged as a keystone for clinical interpretation.¹ The thyroid hormone acts on virtually all organ systems; in particular, the heart responds to minimal changes in serum thyroid hormone level. The wide range of hemodynamic changes and cardiovascular complications that accompany hyperthyroidism serve to highlight the role of thyroid hormone in the physiology of the cardiovascular system. Hence there is a need to investigate all patients for cardiovascular symptoms in newly diagnosed hyperthyroidism, mainly in the elderly.

Overt hyperthyroidism prompts a hyper-dynamic circulatory state (high cardiac output with lesser systemic vascular resistance), which is accompanied with a faster heart rate, enhanced left ventricular systolic and diastolic

function, and increased occurrence of supraventricular tachyarrhythmias.¹ Severely hyperthyroid patients can show symptoms of congestive heart failure in the absence of prior pathology.² As a non-invasive method, echocardiography can play a vital role in recognizing the cardiac pathology in hyperthyroid patients as well as to follow up their response to therapy.

Very limited data are available regarding cardiovascular manifestations in hyperthyroid patients in Indian population. Also most of the previous studies were either cross sectional or retrospective. The present research was a prospective and observational study carried out in tertiary care hospital. The main aim of this study was to evaluate the frequency of different cardiovascular abnormalities in patients

with hyperthyroidism and to observe the changes in these abnormalities with antithyroid treatment.

Material and Methods

Study design

This was an observational and prospective study carried out during September 2013 to August 2014 at Seth G.S.M.C and K.E.M Hospital, Mumbai. Total 96 hyperthyroid patients were screened and those 40 patients were included in study that had symptoms and signs suggestive of cardiovascular system involvement. These patients had a single follow up after 3 months of initial visit.

Both male and female patients more than 12 years of age who had recently confirmed diagnosis of hyperthyroidism by T₃, T₄, TSH levels with symptoms and sign suggestive of cardiovascular system involvement and who agreed to sign the consent were eligible for the study. Patients with known heart diseases like congenital heart disease, rheumatic heart disease, ischemic heart disease etc., those on iodine containing drugs e.g. amiodarone or on treatment for their known hyperthyroid disease in the past and patients with known disease which may alter the total serum thyroid hormones level or CVS manifestations e.g. chronic liver disease, chronic renal disease, hypoproteinemia, severe anaemia and pregnancy were excluded from the study.

Study procedure

The study had included the hyperthyroid patients of more than 12 years of age attending the out-patient department of General Medicine, attending thyroid clinic as well as patients in endocrinology ward of our hospital after obtaining permission of institutional review board and written informed consent of patient.

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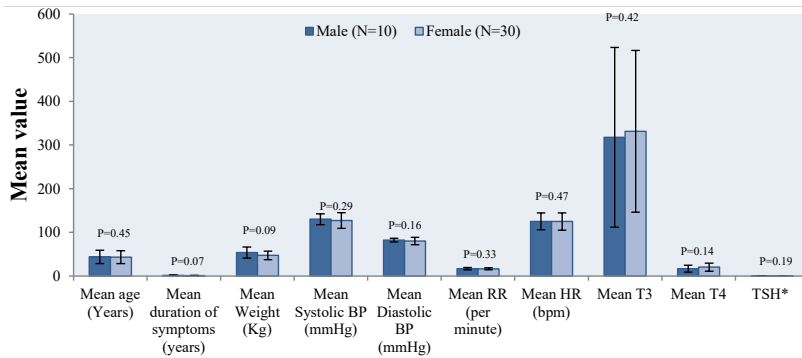


Fig. 1: Comparison of baseline characteristics between male and female patients. TSH* = TSH (of 4 male & 14 female patients) not detectable in remaining 22 patients (6 males and 16 females). RR=Respiratory rate; HR=Heart rate

Individual patients were asked detailed history about the general symptoms of hyperthyroidism, with special emphasis to cardiovascular symptoms, personal habits, occupation and other cardiovascular disease which may alter the result of our study. Detailed physical examination including general and systemic examination was carried out. The routine investigations mandatory for all hyperthyroid patients as well as investigation's done for cardiovascular system involvement were performed. These included, thyroid function test, resting 12-lead electrocardiogram (ECG), 2D ECHO. Hyperthyroid subjects were treated with antithyroid drugs/potassium iodide/beta blockers/radioactive iodine by their respective physician. All these patients were re-evaluated after 3 months of antithyroid therapy.

Information was collected using a case record form. Cardiovascular symptoms had to be of new onset coincident with the onset of hyperthyroidism. Symptoms evaluated included dyspnoea, chest pain, palpitation, orthopnoea, paroxysmal nocturnal dyspnoea, cough and pedal edema. Smoking history was documented. Findings noted on examination included body weight, pulse rate, blood pressure, pedal edema, presence of raised jugular venous pressure, displaced apex beat (beyond 5th intercostal space, mid clavicular line), cardiac murmurs, and abnormal chest auscultation (crepitation's or wheeze). All subjects were evaluated by a single investigator.

Thyroid Function Assessment

Assessment of thyroid function was done from our endocrinology laboratory. The normal range for serum $T_3 = 100 - 200$ ng/dl, $T_4 = 4 - 12$ µg/dl and TSH=0.4 - 4.5 µIU/ml. Anti TPO, thyroid scan and scintigraphy were done

if indicated. TFT was repeated at end of three months.

Cardiac rhythm assessment

The ECG findings were noted as normal, sinus tachycardia, p wave abnormality, abnormal cardiac axis, left or right bundle branch block, left ventricular hypertrophy (LVH), heart block, etc. ECG was again carried out after 3 months and findings were compared with previous findings.

2D ECHO was carried out in Cardiology Department at the recruitment and after the period of 3 months and the findings were compared as before and after 3 months of antithyroid treatment.

Statistical analysis

Appropriate statistics was applied to compare the various parameters before and after treatment using SPSS version 20. Assuming variables a normal distribution were presented as mean \pm SEM. Nominal data were expressed as number and percentage of total.

Results

Mean age at presentation was 43.9 ± 15.26 years for male and 43.23 ± 14.73 years for female. It was nearly same for males and females (Figures 1 and 2). Mean duration of symptoms for female was lower than that for male. It was 15 month's (1.3 years) for males and 7 months (0.68 years) for females. Mean body weight for male was more in male than female. It was 53.6 ± 12.81 Kg for males and 47.27 ± 9.70 Kg for females. Mean systolic / diastolic BP were slightly higher in males than for females. It was $130 \pm 12.26 / 82 \pm 4.21$ for males and $127.13 \pm 17.8 / 79.93 \pm 8.39$ for females (Figure 1).

Mean respiratory rate for both males and females were same i.e. 16.5 ± 2.31 per minute. The mean heart rate at

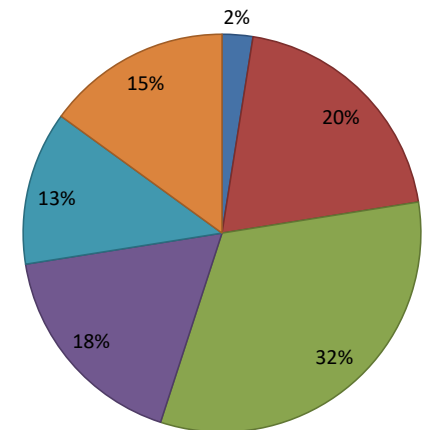


Fig. 2: Age distribution (N=40)

baseline for males was 125.2 ± 19.1 per minute while for females, it was 124.73 ± 19.72 per minute. It was nearly same for both genders.

Mean total serum T_3 level for males and females was 317.60 ± 205.64 and 331.34 ± 185.47 respectively. Mean total serum T_4 level for males and females was 16.82 ± 7.97 and 20.23 ± 9.1 respectively (Figure 1).

The mean serum total T_3 and T_4 level were higher in females as compared to males while serum TSH level was lower in females as compared to males. Serum TSH was not detectable in remaining 22 patients (16 females and 6 males). 31 patients (7 male and 24 female) were overt hyperthyroid i.e. increased serum T_3 and T_4 level and very low or undetectable serum TSH level. Of these, 1 female patient presented with thyroid storm. The remaining patients had subclinical hyperthyroidism i.e. normal serum T_3 and T_4 level and low or undetectable serum TSH level.

In this study, Grave's disease was found to be the most common etiology contributing for 82.5% of hyperthyroid cases, followed by toxic multinodular goiter in 7.5% cases. The less common etiology includes autonomously functioning thyroid lobe (5%), solitary adenoma (3%) and subacute thyroiditis (3%). Toxic multinodular goiter was seen in those patients with age more than 50 years.

In the study the most frequent general complaints observed were generalized weakness, weight loss and tremors (Figure 4). The frequency of tremors was 67.5% in hyperthyroid patient with CVS involvement. Palpitation was the most common CVS symptoms seen in 80% of our patients. Patient had

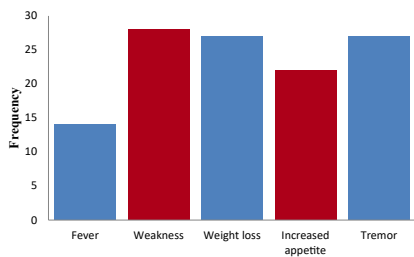


Fig. 3: General complaints (N=40)

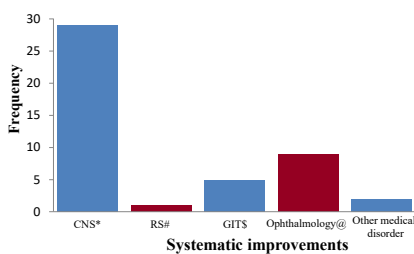


Fig. 4: Other system complaints (n=40). *Includes Insomnia/Irritability/ Nervousness/Anxiety/ Sweating; #Cough; @Diarrhoea; @ Exophthalmos / Diplopia

Table 1: ECG analysis

Parameter	First visit (n=40)	Follow up (n=40)
Normal sinus rate and rhythm	6 (15%)	30 (75%)
Sinus tachycardia	27 (67%)	8 (20%)
Atrial fibrillation	7 (17.5%)	2 (5%)
Left ventricular hypertrophy(LVH)	2 (2.5%)	2 (5%)
Right ventricular hypertrophy(RVH)	1 (2.5%)	1(2.5%)
P pulmonale	1 (2.5%)	1(2.5%)
Conduction block	0	0

palpitation even at rest but more on exertion and was intermittent (Figure 5). After CVS the other system, most commonly affected was nervous system with frequency of 72.5%. Patients mostly presented with irritability, insomnia and anxiety. The next most common symptoms were dyspnoea and chest pain with prevalence of 55% and 37.5% respectively that were not associated with exertion. Chest pain was intermittent, not associated with any abnormal ECG finding suggestive of myocardial ischemia. Cough was prevalent in 32.5% patient.

In our study, tachycardia (pulse rate >100/min) were the most prevalent sign seen in 34 of 40 patient (85%). Of this 34 patient, 27 had sinus tachycardia while 7 patients had atrial fibrillation. ECG abnormality matches with these clinical signs. 2D ECHO had abnormal findings in 12 patients. Only 4 patients show cardiomegaly on chest X-ray. On auscultation, 4 patients had pan systolic

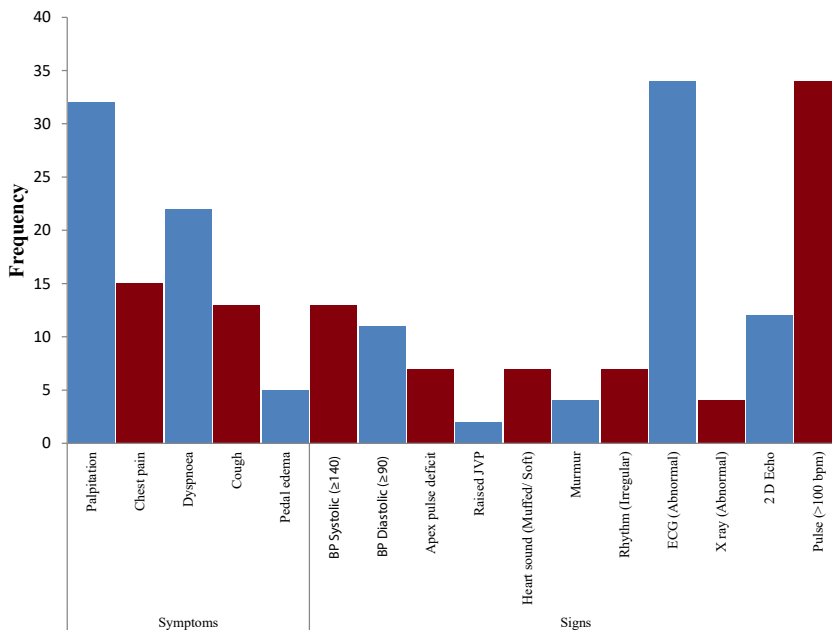


Fig. 5: CVS abnormalities (N=40)

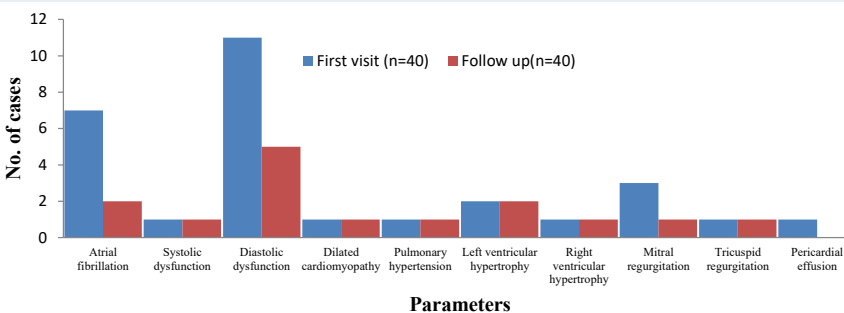


Fig. 6: 2D-ECHO analysis

murmur suggestive of regurgitant valvular lesion.

Thyroid gland was enlarged in only 20 of 40 cases (Prevalence=50%) and exophthalmos was seen in 8 of 40 cases. 1 patient had diplopia secondary to thyroid myopathy.

On first visit 34 of 40 patients (85%) had abnormal ECG findings. The most common ECG abnormality was sinus tachycardia seen in 67% of Patient followed by atrial fibrillation seen in 17.5% patient. The less common findings include LVH, RVH and P pulmonale (Table 1). On follow up only 9 of 40 patients (22.5%) had abnormal ECG findings which include sinus tachycardia in 20% patient while atrial fibrillation seen in only 5% of patient. The other findings persisted.

2D ECHO was done in all 40 patient, 12 of 40 patient show abnormal ECHO findings (Figure 6). 7 patients were detected to have atrial fibrillation. 11 patients had diastolic dysfunction while only 1 patient had systolic dysfunction

out of the above 12 patients, which suggested that diastolic dysfunction was very common in hyperthyroid patient. Of these 11 patients with diastolic dysfunction almost all had heart rate more than 100 beats per minute. The higher heart rates found in hyperthyroid patients shortened the diastolic period of cardiac cycle hence decreasing the end diastolic volume. On follow up, 5 of 12 patients had diastolic dysfunction. Of these 5 patients, almost all had heart rate of more than 100 beats per minute. Hypertension was seen in 32.5% of patients. Atrial fibrillation was seen in 17.5% patient. Heart failure was shown in 12.5% patient and valvular involvement found in 3 patients (7.5%) in the form of functional mitral regurgitation. Only 1 patient (2.5%) had dilated cardiomyopathy in our study.

In our study, a statistically significant positive correlation was found between T₃ and T₄ level and pulse rate while there was weak negative correlation

Table 2: Correlation between pulse rate, blood pressure and the level of serum T₃, T₄ and TSH

	T3	T4	TSH
Systolic blood pressure	0.092243	0.254635	-0.09212
Diastolic blood pressure	0.187312	0.249043	-0.26842
Heart rate	0.63537	0.747519	-0.13619
Strength of relationship (- is for negative correlation)			
Value of r (Correlation coefficient)	Strength of relationship		
-1.0 to -0.5 or 1.0 to 0.5	Strong		
-0.5 to -0.3 or 0.3 to 0.5	Moderate		
-0.3 to -0.1 or 0.1 to 0.3	Weak		
-0.1 to 0.1	None or very weak		

between TSH level and pulse rate ($r = -0.13619$). Serum T₃, T₄ and pulse rate had strong positive correlation with Correlation coefficient (r) of 0.63537 and 0.747519, respectively (Table 2).

Patient with higher serum T₃ and T₄ level had a higher pulse rate as shown in above graphs. On follow up, pulse rate also decreased with decreased serum T₃ and T₄ level. Patients who had persistently higher serum T₃ and T₄ level also had higher pulse rate as compared to those with normal T₃, T₄ level. In our study, there was weak positive correlation between systolic and diastolic blood pressure and serum T₃, T₄ level with correlation coefficient of 0.092243 and 0.254635 for systolic BP and 0.187312 and 0.249043 for diastolic BP. Also change in blood pressure of our patient was not statistically significant. On recruitment, 7 patients had atrial fibrillation. In 5 of 7 these patients, T₃ levels were more than 400 ng/dl and T₄ levels were more than 20 µg/dl. TSH was not detectable in all of them. It shows that those patients who had higher T₃ and T₄ levels were more prone to atrial fibrillation.

On follow up, only 2 patients had atrial fibrillation. The frequency of atrial fibrillation was significantly reduced (p value=0.0324). In 1 of this 2 patients, serum T₃ level was still more than 400 ng/dl and T₄ level was in between 15-20 µg/dl. Serum TSH was not detectable in both of them.

On follow up after 3 month of treatment, tremors were significantly reduced with p value of <0.0001. Also there were significant reductions in cardiovascular symptom like palpitation, chest pain, cough, dyspnoea and the reduction were statistically significant.

On follow up, a statistically significant reduction were seen in

pulse rate and ECG abnormality with p value of <0.05. Other parameter's like blood pressure, X-ray abnormality, and ECHO findings did not significantly reduce.

31 of 40 patients were overt hyperthyroid (1 patient had presented with thyroid storm), while 9 patient were subclinical hyperthyroid on recruitment. After 3 month of treatment, 28 patients (70%) became euthyroid, 4 patients (10%) were subclinical hyperthyroid, and 7 patients (17.5%) had persistent overt hyperthyroid state. 1 of these 40 patients who had subclinical thyroiditis at baseline became hypothyroid. This patient did not receive any anti thyroid drugs.

Discussion

The present findings of our study clearly indicate that hyperthyroidism is more prevalent in females as compared to males by supporting the statement that female sex was a strong risk factor throughout the entire span of ages for the development of overt hyperthyroidism with CVS involvement. These results are similar to the study conducted by Jack and Osman et al.^{3,4}

In this study, out of 40 patients, 31 had overt hyperthyroidism and 9 had subclinical hyperthyroidism. Of these 40 patients, 82.5% had Grave's disease, an autoimmune disorder which is the most common etiology of hyperthyroidism with 50-80% distribution worldwide, and this is thought to be due to varying levels of iodine in the diet.⁵ The role of Iodine deficiency on the prevalence of hyperthyroidism and Graves' disease was proved by a study conducted Allan et al.⁶

In our study out of 40, 34 hyperthyroid patients received Neomercazole and beta blocker (propranolol), 5 patients received Neomercazole alone and remaining 1 received propranolol only. Potassium iodide was given to 1 patient who presented with thyroid storm. After 3 month of follow up, 7 patients remained overt hyperthyroid, 4 showed the biochemistry of subclinical hyperthyroidism, 28 patients were rendered biochemically euthyroid at the time of re-evaluation while 1 patient became hypothyroid and the improvement in patients were very good compared to the earlier studies done by Osman et al in Birmingham, England from April 1999 to April 2002⁴.

Cardiovascular symptoms and signs were more prevalent in hyperthyroid

patients. Palpitation was the most common cardio-vascular symptoms seen in 32 of 40 (80%) patients followed by dyspnoea in 22 patients, followed by chest pain, cough and pedal edema seen in 15, 13 and 5 patients respectively. After 3 month of treatment the patients became euthyroid and these symptoms significantly reduced (p value <0.05). Successful management of the hyperthyroidism has been accompanying with a reversal of these symptoms as documented in literature and previous studies.^{4,7}

In cases of severe and chronic hyperthyroidism, exaggerated sinus tachycardia or atrial fibrillation can generate rate related left ventricular dysfunction and cardiac failure. This explains the observation that many patients with the association of hyperthyroidism, decreased cardiac output, and impaired left ventricular function are in atrial fibrillation at the time of diagnosis.^{8,9} AF occurs in up to 15% of patients with hyperthyroidism¹⁰ compared with 4% incidence in the general population¹¹ and is more common in male patients with triiodothyronine (T₃) toxicosis. Earlier studies found that dysrhythmias is prevalent in hyperthyroid patients.^{12,13} But ventricular dysrhythmias were not more prevalent in hyperthyroidism in the present study.

In this study, out of 40 patients investigated by ECG, 34 patients had abnormal ECG findings. The most common ECG finding was sinus tachycardia seen in 67% followed by atrial fibrillation seen in 17.5% patients. On follow up, only 10 of 40 patient showed abnormal ECG pattern, of these 20% patients had sinus tachycardia and only 5% patients had atrial fibrillation and the overall reversal of ECG abnormality i.e. sinus tachycardia, atrial fibrillation etc. that was statistically significant (p value <0.0001). These findings in our study are similar to the observations of Yamamoto et al.¹⁴

In our study 2D ECHO was done in all patients at recruitment and after 3 month of follow up. During recruitment 12 of 40 patient (30%) show abnormal ECHO findings. The most common abnormal ECHO finding were diastolic dysfunction seen in 11 of 12 patients with one patient having systolic dysfunction. Ansari et al conducted similar study on 69 patients and they correlated echocardiographic findings with ECG and chest radiograph¹⁵. The frequency of atrial fibrillation found in

Table 3: Response to anti-thyroid treatment at the end of 3 months to cardiovascular symptoms

Symptom	Before treatment (n=40)	After treatment (n=40)	P value
Tremors	27	2	<0.0001
Palpitation	32	7	<0.0001
Chest pain	15	2	0.0007
Dyspnoea	22	11	0.021
Cough	13	2	0.0031
Pedal edema	5	1	0.2007

Table 4: Response to anti-thyroid treatment at end of 3 months to cardiovascular signs

Signs	Before treatment (n=40)	After treatment (n=40)	P value
Pulse (>100)	34	8	<0.0001
Rhythm (Irregular)	7	2	0.0324
BP Systolic (≥140)	13	5	0.0609
BP Diastolic (≥90)	11	8	0.5993
Apex pulse deficit	7	2	0.0324
JVP	2	1	1
Heart sound (Muffled/Soft)	7	2	0.0324
Murmur	4	2	1
ECG (Abnormal)	34	9	<0.0001
X-ray (Abnormal)	4	3	1
2 D Echo	12	7	0.2933

our study was nearly same with their findings. After 3 month of follow up, 5 of 12 patients had diastolic dysfunction while 1 patient had depressed LV systolic function. 2 patients were still in atrial fibrillation. 2 of 3 patients who previously had mitral regurgitation reversed to normal. These 2D ECHO abnormalities which improved after restoration of euthyroid state were functional rather than structural. The structural abnormalities like dilated cardiomyopathy, LVH, RVH, pulmonary hypertension persisted. The overall 2D ECHO abnormalities did not significantly improve. The above findings suggest that once the structural changes occurred in cardiac tissue, they do not improved much even if patients became euthyroid. This was in accordance with the studies of Smit et al.¹⁶

In the present study, a positive correlation was found (which was statistically significant) between serum T₃ and T₄ level and pulse rate while there was weak negative correlation between

Table 5: Thyroid status at baseline and on follows up

	First visit (n=40)	Follow up (n=40)			
		Overt hyperthyroidism	Subclinical hyperthyroid	Euthyroid	Hypothyroid
Overt hyperthyroid	30 (75%)	6	4	19	1
Subclinical hyperthyroid	9 (22.5%)	0	0	9	0
Thyroid storm	1 (2.5%)	1	0	0	0
Total no. of patient	40 (100%)	7 (17.5%)	4 (10%)	28 (70%)	1 (2.5%)

S.TSH level and pulse rate ($r = -0.13619$) as given in Table 4 which matches with a study conducted in Iraq by Abas et al.¹⁷ Patient with overt hyperthyroidism had a higher pulse rate as compared to those with subclinical hyperthyroidism. Also atrial fibrillation was seen in those patients who had serum T₃ level of more than 400 ng/dl and did not show any structural abnormality on 2D ECHO suggesting that atrial fibrillation was due to the direct influence of the thyroid hormone on the heart. As these patients became euthyroid, the frequency of atrial fibrillation decreased significantly. These findings in our study suggests that patients with overt hyperthyroidism were more prone for the development of atrial fibrillation than those with subclinical hyperthyroidism and patient may restore the sinus rhythm once the serum thyroid hormones levels were normalised.

Conclusion

Our study concludes that cardiovascular system involvement was observed in 40% of hyperthyroid patients. It was found that the prevalence of hyperthyroidism with cardiovascular involvement was more in females as compared to males. The most common cause of hyperthyroidism was Grave's disease (82.5%) followed by toxic multinodular goitre. Sinus tachycardia was the most common clinical sign as observed in ECG findings (67%) followed by atrial fibrillation. Systolic hypertension was more common than diastolic hypertension in our study and reduction in blood pressure was not statistically significant with treatment even at the end of 3 month. Diastolic dysfunction was the most common 2D ECHO abnormality seen in 11 of 40 patients.

Clinical symptoms and signs such as tremors, tachycardia, atrial fibrillation significantly improved with antithyroid treatment and the improvement in these finding were statistically significant. Hyperthyroid patients who rendered euthyroid with treatment showed

significant relief in their symptoms as well as ECG abnormality but some 2D ECHO abnormalities persisted. As our study had a short follow up of 3 months only, further follow up is needed to confirm the persistence of these 2D ECHO abnormalities.

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