Cardiovascular Manifestations of Primary Hypothyroidism

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ABSTRACT:

BACKGROUND:

Primary hypothyroidism accounts for 90 to 95 %of all cases of hypothyroidism. Thyroid hormone deficiency increases systemic vascular resistance, decreases contractility and slow the heart rate .

OBJECTIVE:

To investigate cardiac changes in primary hypothyroidism.

METHODS:

In this prospective study 36 patients with untreated primary hypothyroidism were compared with 30 healthy persons. Cardiovascular evaluation of all subjects had been made both clinically and by the following studies :Chest X-Ray, electrocardiography, serum lipid and Echocardiography.

RESULTS:

The main cardiac manifestations of hypothyroidism were: Easy fatigability) 88.9%), exertional dyspnea (75%o),obesity or gaining weight(66.7%), sinus bradycardia (47.2%)and peripheral edema(11.1%)Electrocardiography showed sinus bradycardia in(47%) low QRS voltage in (33.3%) , flat or inverted T wave(27.8%), prolonged QT interval (19.5%), first degree heart block in(19.5 %) .Echocardiography showed the following :a decrease in global systolic function, asymmetric sepal hypertrophy in (91.6%) Pericardial effusion in (38.8%).Low QRS voltage was found to be related to thyroxin level and age of the patient .No correlation was found between heart rate and thyroxin level.

CONCLUSION:

Primary hypothyroidism accompanied by significant changes in cardiovascular system which may explain the development of premature coronary artery disease in these patients.

KEYWORDS: primary hypothyroidism, cardiovascular manifestations.

INTRODUCTION:

Hypothyroidism is the clinical syndrome that results from decreased secretion of thyroid hormone form the thyroid gland .It most frequently reflects a disease of the gland itself (primary hypothyroidism) but can also be caused by pituitary disease secondary hypothyroidism or hypothalamic disease)tertiary hypothyroidism) [1] .

The incidence of hypothyroidism peaks between the ages of 30 and 60 years[2]. The female: male ratio is approximately 6: 1[3] .Primary hypothyroidism accounts for 90 to 95 %of all cases .Most patients develop hypothyroidism during adulthood) 1 .However, the majority of cases are due to chronic autoimmune (Hashimoto's) thyroiditis, radioactive iodine therapy and surgery[4] .

The most common cardiac signs are bradycardia, mild hypertension, a narrowed pulse pressure and attenuated activity on the precordial examination . Other characteristics but non-specific findings are high serum concentrations of cholesterol and creatine kinase .Pericardial effusion and non-pitting oedema can occur in patients with severe long standing hypothyroidism .In spite of low cardiac output, heart failure is rare, because the cardiac output is usually sufficient to meet the lowered demand for peripheral oxygen delivery[5,6].

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SUBJECTS AND METHODS :

Over a period of eighteen months (from Jan .2000 -Jul 2001), a total of 36 consecutive patients (31 females and 5 males with a female to male ratio 6.2 :1) (with a mean age of 44 ± 13 years ranging from 19-67 years) with untreated primary hypothyroidism were enrolled in this prospective study .All patients had been seen at Baghdad Teaching hospital, Baghdad .None of the patients had history of congenital or rheumatic heart disease and none of them were receiving digitalis, β-adrenergic blocking drugs or other cardiovascular or anti-arrhythmic drugs and none of them had history of amiodarone ingestion .Full clinical evaluation was done for each patient)full history and physical examination .(The following investigation were done for each patient within two weeks of drawing blood for serum T4 and TSH assay:Electrocardiography)ECG, chest X-ray, echocardiography, total serum cholesterol and serum triglycerides.Thirty patients had spontaneous primary hypothyroidism and six developed hypothyroidism after Iodine therapy .The diagnosis

was based on typical clinical symptoms and confirmed by biochemical tests)low free serum T4, high TSH levels.

Controls group consisted of 30 healthy persons (26 females and 4 males with a mean age of 42 ± 13 years ranging from 12-65 years) who were healthy volunteers .None of them had any symptom or history of thyroid or cardiovascular disease and none was taking any medication.Full clinical evaluation was done for each person .In addition to the following tests :ECG, CXR, echocardiography, total serum cholesterol and serum triglycerides.

Hormone assays :Blood from the patients was drawn in a fasting state for the determination of total thyroxin (T4)and thyroid stimulating hormone (TSH) assay.Total thyroxin levels were measured by a radioimmunoassay using ^{125}I (total T4 radioimmunoassay kit)Diasorin, Stillwater, MN 55082 U.S.A(the normal range is 6.1-11.8 ug/dl).Serum thyroid stimulating hormone levels were measured by a radioimmunoassay using (I) hTSH radioimmunoassay kit)Diasorin, Stillwater, MN 55082 U.S(the normal range is 0.4-3.1 ulU/ml).Primary hypothyroidism was defined as elevated thyroid stimulating hormone levels > 20 ulU/ml associated with low levels < 6.1 ug/dl of serum thyroxin[1,3,16,18].

Serum lipids :Blood from both the patients and controls was drawn after fasting 14 hours for the determination of total blood cholesterol and serum triglycerides .They were measure at Teaching Laboratories ,Baghdad Teaching Hospital.

Enzymatic determination of cholesterol was performed using cholesterol enzymatique (PAP kit)bioMerieux SA /69280 Marcy-I'Etoile /France . Serum triglycerides were measured using triglycerides Enzymatique (PAP-150 kit) bioMerieux SA /69280 Marcy-I'Etoile /France.

Echocardiographic studies: The studies were done with a Voluson 530 D (Kretz technik/Austria) equipped with a 2.5 MHz transducer .All studies were performed during normal quiet respiration . Two-dimensional and M-mode tracing were obtained in the parasternal window in the slight left lateral position .Five consecutive sinus beats were measured and averaged .Cursor-derived M-mode recordings obtained during two-dimensional echocardiographic examinations were used to validate electronic measurements.

The following echocardiographic measurements were studied for the patients and controls[14] ejection fraction(%), fractional shortening(%),diastolic interventricular septal thickness normal range:6-11mm, diastolic left ventricular posterior wall thickness)normal range : 6-11mm(IVS /LVPW ratio) Asymmetric septal hypertrophy defined as a ratio > 1.3, presence or absence of pericardial effusion.

Electrocardiography (ECG):After resting for 30 minutes, standard 12-leads ECG was obtained for each one in the patients and control groups .

Chest X-ray examination: Was taken in full inspiration and upright position .cardiac enlargement was considered when the cardio-thoracic C/T (ratio > 50 percent) .

Statistical analysis: All parameters were measured by using number, percent and mean +SD .The association between parameters was measured by using Chi square test and t-test.The association was considered significant when P-value<0.05 .The relationship between heart rate and thyroxin(T4) level was measured by using correlation coefficient.

RESULTS:

Table 1 :shows age and sex characteristics of patients and control groups.

Table 1 :Demographic characters (age and sex)of studied sample

Character	Patients group	Control group	P-Value
(Age)year (n)mean ±SD	(36)44.39±13.27	(30)42.63±13.57	NS*
Sex Male n(%) Female n(%) Total n(%)	 (5)13.9 (31)86.1 (36)100(%)	 (4)13.3 (26)86.7 (30)100(%)	NS**

*P-value using t-test **P-value using Chi square test

Our study shows that the main clinical cardiac manifestations in hypothyroid patients were :Easy fatigability 32/36 (88.9%) , Exertional dyspnea 27/36 (75%), obesity or gaining weight in 24/36) 66.7(%, sinus bradycardia in 17/36 (47.2 %), pericardial effusion in 14/36 (38.9 %), angina in 4/36 (11.1 %), peripheral oedema in 4/36 (11.1 %) orthopnoea in 2/36 (5.6 %) and paroxysmal nocturnal dyspnoea in 2/36 (5.6 %) patients . Ascites, weak arterial pulse and xanthelasma were occasional finding and each was detected in one patient only.

This study shows a statistically significant difference)P < 0.05 (in the heart rate of patients compared with the control .The mean heart rate in the patients group was 61 beat per minute .

Bradycardia)heart rate < 60 (was detected in 17/36 (47.2 %) of the patients.We found a statistically significant difference)P < 0.05 (of the diastolic blood pressure in patients (mean ± SD) (79.65+9.17) compared to the control .No statistically significant difference was observed regarding systolic blood pressure in patients(mean ± SD) (122.22+15.56) compared to the control .
Cardiac enlargement)as measured by cardiothoracic ratio in chest X-ray (was found in 12/36 (33.3%) of the patients and all of them had evidence of pericardial effusion by echocardiography. This difference was statistically significant (P < 0.05). A statistically significant (P< 0.05) higher total serum cholesterol and triglyceride levels of the patients compared to the control was observed (261.53 ± 80.83 and 170.50 ±51.55 versus 182.30 +33.21 and (119.97 ±19.04) Table2.

Table 2 : Comparison between lipid levels of patient and control groups

Type of lipid	(Patient group n)mean ± SD	(Control group N)mean ±SD	P-value *
Total cholesterol level	(36)261.53±80.83	(30)182.30±33.21	<0.05
Triglycerides level	(36)170.50±51.55	(30)119.97 ±19.04	<0.05

P-value by t-test

(Table)3 (shows the electrocardiographic findings of patients.The study shows a statistically significant difference)P < 0.05 (regarding the presence of sinus bradycardia in patients compared to the control (47.2 %versus 6.7%).A statistically significant difference (P < 0.05) was observed regarding the presence of low QRS voltage in patients compared to the control (33.3%) versus zero.(A statistically significant difference (P < 0.05)was found regarding the presence of flat or inverted T-wave in patients compared to the control (27.8 %versus 3.3 %).A statistically significant difference (P < 0.05)was observed regarding the presence of first degree heart block in patients compared to the control (19.5 %versus zero).No statistically significant difference was observed regarding the presence of left anterior hemiblock (LAH)in patients compared to the control.A statistically significant difference (P < 0.05)was observed regarding the prolonged QTc in patients compared to the control (19.5 %versus zero).

Table 3: Comparison between electrocardiographic findings of patient and control groups

			Patient groupn (%)	Control group n (%)	P-value *
Sinus bradycardia		Absent Present	19(52.8) (1747.2)	28(93.3) 2 (6.7)	P<0.05
Flat or inverted T-wave		Absent Present	26 (72.2) 10(27.8)	29(96.7) 1(3.3)	P<0.05
Low QRS voltage		Absent Present	24(66.7) 12(33.3)	30(100) 0(0)	P<0.05
Conduction disturbance	First degree heart block Absent Present Left anterior hemiblock Absent Present		 29(80.5) 7(19.5) 33(91.6) 3(8.3)	 30(100) 0(0) 30(100) 0 (0)	P<0.05 NS
QTc interval		Normal Prolonged	29(80.5) 7(19.5)	30(100) 0(0)	P<0.05

Chi-square test

Our study shows a statistically significant(P < 0.05)lower ejection fraction and fractional shortening values in the patients compared to the control group (mean ± SD) (.51.97 ±9.10 and 23.33 ±10.16 versus 60.77 ± 5.90 and 29.70 ± 7.80 respectively). Interventricular septum (IVS) dimension and the ratio of (IVS /LVPW)were significantly (p < 0.05) higher in patients compared with the control group (mean ± SD) .(15.08 ± 2.99 and 1.56 ± 0.23 versus 9.79 ± 1.61 and 1.11 ± 0.13 respectively) .Asymmetric septal hypertrophy (IVS /LVPW > 1.3) was fond in 33/36 (91.6%) of the patients .No statistically significant difference was observed regarding the left ventricular posterior wall thickness (LVPW) in patients compared to the control Table 4.

Table 4 : Comparison between echocardiographic findings of patients and control groups

	Patient group n (mean ± SD)	Control group n(mean ± SD)	P-value *
Ejection fraction (%)	36(51.97±9.10)	30(60.77±5.90)	<0.05
Fractional shortening (%)	36(23.33 ±10.16)	30(29.70 ±7.80)	<0.05
IVS (mm) LVPW (mm) IVS /LVPW	36(15.08 ±2.99) 36(9.67±1.13) 36(1.56 ±0.23)	30(9.79 ±1.61) 30(9.47 ±1.37) 30(1.11 ±0.13)	<0.05 NS <0.05

*t-test

No statistically significant relationship was observed between the occurrence of pericardial effusion and the heart rate in studied patients .No statistically significant relationship was observed between the occurrence of pericardial effusion and the thyroxin level in the studied patients(Table 5.)

Table 5 : Relationship between the occurrence of pericardial effusion and the heart rate and pericardial effusion with thyroxin blood level in hypothyroid patients

	Pericardial effusion			P-value *
	Absent n (mean ± SD)	Present n (mean +SD)	Total n(mean ± SD)	
Heart rate	22 (63.41±7.44)	14(59.21±9.32)	36(61.78±8.36)	NS
Thyroxin level(T4)	22(2.17±1.10)	14(2.05±1.08)	30 (2.12±1.08)	NS

t-test

In this study no statistically significant association was found between the occurrence of pericardial effusion and QRS voltage value .Patients with low QRS voltage had statistically significant ($p < 0.05$) older age than those with normal QRS voltage (mean +SD) (.53.33 ± 8.36 versus 39.92 ±13.18.(Thyroxin level was significantly lower ($p< 0.05$) in patient with low QRS voltage compared with those who had normal QRS voltage value (mean ± SD) (.1.40 ± 0.64 versus 2.49 ± 1.08 respectively) Table 6.

Table 6 : Association between low QRS voltage and each of pericardial effusion, thyroxin level and age in hypothyroid patients

	QRS voltage		Total
	Normal	Low	
Pericardial effusion Absent n (%) Present n (%)	١٧(77.3) 7(50.0)	5) (22.7) 7(50.0)	22(100.0) 14 (100.0)
Total n(%)	24(66.7)	12(33.3)	36 (100.0)

Chi square test NS

	QRS voltage			P-value
	Normal	Low	Total	
	n(mean ± SD)	n (mean ± SD)	n(mean ± SD)	
Age	٢٤ (39.92 ±13.18)	12(53.33 ±8.36)	36(44.39±13.27)	<0.05
Thyroxin level(T4)	24(2.49 ±1.08)	12(1.40 ±0.64)	36(2.12 ±1.08)	<0.05

t-test

Although we found that there is a positive relationship between heart rate and thyroxin level r + =0.210 it was not found to be significant when thyroxin (T4)level was below normal ($P > 0.05$) Table 7

Table 7: Correlation between heart rate and thyroxin(T4) level in hypothyroid patients

	n	r	Significant
Heart rate and T4	36	±0.210	NS

No statistically significant correlation

DISCUSSION:

In the present study, the age of patients with primary hypothyroidism ranging from 19-67 years (with a mean age of 44 years) .Most of the patients were between 30-60 years which agrees with the results in other studies[1,7,8] .Sex distribution of our hypothyroid patients showed female :male ratio of 6.2 :1 (table 1) .This result agrees with that found in other studies[1,3,7,8,9,10] . No statistically significant difference in the age and sex characters of the patients and control was found (age and sex matched control groups).

The main cardiovascular manifestations in the present study in decreasing order of frequency were: easy fatigability, exertional dyspnoea, obesity and weight gain, sinus bradycardia, pericardial effusion, angina and peripheral oedema . These findings agree with that of other workers [1,2,7,11] .

This study shows a statistically significant lower heart rate of patients compared with the control groups .This finding agrees with the universal concept about slower heart rate in patients with hypothyroidism [1,2,3] .

In the present study, 7/36 (19.5 %) patients had diastolic blood pressure over 90 mmHg, five of them(71.42 %)were above 50 years .A statistically significant higher diastolic blood pressure values in patients compared with the control was observed . However, only 2/36 (5 %) of the patients had systolic blood pressure above 140mmHg and no statistically significant difference was observed in the systolic blood pressure between the patients and the control groups .These results are comparable with those given by another study (14%)[12] .These figures suggest that patients with primary hypothyroidism have an increased possibility of developing diastolic but not systolic hypertension particularly in those patients over 50 years[13] . The mechanism of increased blood pressure in hypothyroidism is attributed to the acceleration of structural change of vascular tissue by thyroid hormone deficiency which causes a higher total peripheral resistance[14] .

Cardiac enlargement was found in 12/36(33.3%) of the patients, all of them showed evidence of pericardial effusion by echocardiography . Accordingly, it can be concluded that cardiac enlargement still represent a common finding in hypothyroid patients and the radiological enlargement of the heart is usually associated with the presence of pericardial effusions.This conclusion agrees with the generally accepted observation of the occurrence of cardiac enlargement in myxoedema[1,2,11,15] .

Primary hypothyroidism is accompanied by significant changes in serum lipids[1,2,11] .A statistically significant higher total serum cholesterol and serum triglyceride levels of the patients compared with the control group was observed in the present study (mean ± SD) .261.53 ± 80.83 and 170.50 ± 51.55 versus 182.30 ± 33.21 and 119.97 ± 19.04 respectively) .This finding is consistent with that given by other authors in this field of the study[1,2,3,11,16,1718,19,20] .

Hypothyroid patients had significant electrocardiographic changes .A statically significant difference in the occurrence of sinus bradycardia in patients compared to the control groups (47.2 %versus 6.8%) .In other studies, sinus bradycardia reported in)20 -40 (%of the hypothyroid patients[12,21] .

The presence of flat or inverted T waves was significantly different in the patient group compared with the control group)27.8 %versus 3.4%o .(This finding is comparable with that of the other studies which gives a range between(25 - 35 %)[21,22 .] Low QRS voltage was detected in (33.3 %)of the patients .Similar result was reported by other studies[22,23]A statistically significant prolongation of the QTc interval was found in (19.5%o)of the studied patients which agree with the figure found in another study when QTc interval prolongation was found in (20 %)of the hypothyroid patients[13] A statistically significant first degree heart block was found in (19.5) %of the patients which is comparable with the result of another study(12%) [25] .

This study demonstrates a decrease in global systolic function as measured by ejection fraction and fractional shortening and a statistically significant difference was found in both ejection fraction and fractional shortening between patients and the control groups (table 4) .The same finding was reported other studies [26,27] However, different figures was reported by other studies [8,28,29,30] . which have found no decrease in contractility as measured by fractional shortening and ejection fraction .Asymmetric septal hypertrophy was identified in 33 /36 (91.6%) of patients .The mean IVS /LVPW ratio was(1.56 ± 0.23)with a statistically significant difference from the control groups (1.11 ± 0.13).This difference was due to the difference in mean IVS thickness between patients and control groups because there was no difference in mean LVPW thickness between the two groups . These findings agree with the findings of other studies[9,10], but another study reported that asymmetric septal hypertrophy was unusual echocardiographic finding in hypothyroid

patients [8] .This is because the earlier studies were conducted when the diagnosis of hypothyroidism suspected from the presence of classic clinical features .However, recently the diagnosis is usually established in the early or asymptomatic stage in patients because of more frequent determination of thyroid function tests especially in the elderly [31] . For the same reasons, the results in this study were comparable to the earliest studies rather than recently conducted studies because thyroid function tests usually requested for our patients in the presence of classic clinical features .This is partly because thyroid function tests are not available in all hospitals and when available it is relatively costly.

In the present study, pericardial effusion was found in 14/36(38.8 %)patients (table 5), but no cardiac tamponade was detected in any patient which may be explained by gradual accumulation of the effusion[1,11] This result is comparable with that of another study, in which pericardial effusion was detected in(44.4%) [31] Variable figures was reported by other studies ranging from(30 -88 %)[32,33] . No statistically significant associated was found between the occurrence of pericardial effusion and thyroxin level)T4 (in hypothyroid patients .This finding was given by other studies [33,34] . No statistically significant relationship was observed between the occurrence of pericardial effusion in studied patients and the heart rate.

No statistically significant association was found between the occurrence of low QRS voltage and the presence of pericardial effusion (table 6).This result is comparable to that of another study[31] . Another study found that low QRS voltage was related to large pericardial effusion [23] .This study found that low QRS voltage was related to the low thyroxin(T4)levels and to the age of the patients; patients over 50 years had low QRS voltage more frequently than those less than 50 years .Similar result was found by another study[23] .

Although patients with hypothyroidism low (T4) have slow heart rate, but thyroxin level dose not correlate with heart rate(table 7) .

CONCLUSION:

Most of hypothyroid patients in this study presented with the classical features of hypothyroidism because thyroid function tests usually requested to confirm the diagnosis of hypothyroidism not for screening for the condition because it is costly and not available in all hospitals .Primary hypothyroidism accompanied by significant changes in cardiovascular system which may explain the development of premature coronary artery disease in these patients.

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