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Original Work

Effect of levothyroxine therapy on hypertension in hypothyroid patients

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ABSTRACT: The aim of this study was to observe whether levothyroxine replacement therapy has an effect on hypertension in patients of hypothyroidism. This prospective study included all newly diagnosed cases of hypothyroidism (overt or subclinical) with hypertension, of either sex between 21-70 years of age. Levothyroxine replacement therapy was administered continuously during study period. Patients were clinically assessed for blood pressure before and every 3-4 monthly on levothyroxine therapy. Statistical analysis was carried out using a paired Student's t-test. During one year study period, out of 180 newly diagnosed hypothyroid cases enrolled, 88 had overt hypothyroidism (OH) and 92 subclinical hypothyroidism (SH). Male: female ratio was 1: 6.5. Of these, hypertension was present in 51 (28.33%) patients (33 OH and 18 SH). Only diastolic blood pressure was raised in 28(54.9%) cases, systolic in 12 (23.53%) and both systolic and diastolic in 11 (21.57%) cases. Incidence of only diastolic hypertension was comparatively more in overt hypothyroidism (57.57%) than subclinical hypothyroidism (50%). Complete reversal of hypertension was observed in 8 out of 17 SH and 18 out of 29 OH cases while partial reversal was noted in one case in each category. A statistically significant decrease in mean values of both systolic and diastolic blood pressure was observed in patients of SH as well as OH. Hypertension is fairly common in patients of hypothyroidism. Replacement therapy with levothyroxine is quite helpful in reversing hypertension, a potential cardiovascular risk factor.

KEY WORDS: ***Hypertension; Hypothyroidism; Levothyroxine therapy***

INTRODUCTION

Hypothyroidism is a syndrome resulting from deficiency of thyroid hormones namely thyroxine (T_4) and tri-iodothyronine (T_3). Patients having elevated thyroid stimulating hormone (TSH) and low T_3 and T_4 values than normal have overt hypothyroidism (OH), and those with elevated TSH level but normal T_3 and T_4 hormone levels have subclinical hypothyroidism (SH). Overt hypothyroidism is diagnosed when serum concentration of TSH is at or above 10 mμ/litre with a low serum thyroxine (T_4) level, while patients with TSH levels between 4 and 10 mμ/litre and serum tri-iodothyronine (T_3) and T_4 within normal population-based reference range are defined as having mild or subclinical hypothyroidism.[1]

Hypothyroidism has been recognized as an important but an overlooked cause of secondary hypertension. An elevated blood pressure, increased peripheral vascular resistance and low cardiac output have been suggested to be the possible link between hypothyroidism and diastolic hypertension.[2] Almost one third of all cases of myxoedema lead to secondary hypertension. In fact, hypertension is more common in hypothyroid

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patient than in hyperthyroidism. Diastolic hypertension is more commonly seen than systolic hypertension mainly because of increased peripheral resistance.[3-6] Restoration of euthyroidism with thyroxine therapy results in a substantial reduction in both systolic and diastolic blood pressure.[7]

The present study has been undertaken, to observe the incidence of hypertension in cases of hypothyroidism and effects of levothyroxine therapy on hypertension in these patients. Further, to observe whether concurrent replacement therapy with levothyroxine in hypothyroid patients having HT required lesser doses and/or number of antihypertensive drugs.

METHODOLOGY

During one year study period (October 2006 to September 2007), all clinically suspected cases of hypothyroidism in the age group of 21-70 years, of either sex were screened for T3, T4 and TSH values. Based on their values, patients were classified either as OH or as SH. Those patients having normal thyroid profile were excluded from the study. After initial screening (first visit) blood pressure was measured at least twice during two separate examinations before categorizing the patient as hypertensive (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg). Only newly diagnosed hypothyroid patient exhibiting HT in the age group of 21-70 yrs were included in the present study. Patients who were afflicted with chronic ailments like T.B, diabetes, arthritis, ischaemic heart disease or CHF were excluded for the purpose of the study.

Name, age, sex, rural/urban habitat, clinical manifestations, height, weight, body mass index, blood pressure and history of concurrent illnesses were also recorded.

Patients with OH were administered orally 50 to 100 µg / day and those having SH 25 to 50 µg/day of levothyroxine with the goal of normalizing TSH. Patients were subsequently monitored and re-assessed at 3-4 months (first follow-up), at 6-7 months (second follow-up) and at 9-10 months (third follow up) for blood pressure reversal / regression / resurgence.

Comparison was done between systolic and diastolic blood pressures of baseline and first follow-up and between that of baseline and third follow-up. Statistical analysis was carried out using a paired Student's t-test.

RESULTS

Out of a total of 4,697 patients attending the endocrinology outpatient department during the study, 232 were clinically suspected of hypothyroidism. Of these, 52 cases showed a normal thyroid profile and were excluded. The incidence of hypothyroidism was 3.83% (180 out of 4,697). The incidence of SH was 92 (1.96%) and OH was 88 (1.87%) cases. Male: Female ratio was 1:6.5.

Out of 180 patients of hypothyroidism, 51(28.33%) patients were hypertensive comprising of 18 (19.75%) cases of SH and 33 (37.5%) cases of OH. Incidence of hypertension (systolic, diastolic or both) was more common in patients of OH 33 (64.71%) cases. Only diastolic hypertension was comparatively more in both the groups of hypothyroidism (9 out of 18 SH and 19 out of 33 OH). **Table-1**

Overall, replacement therapy with levothyroxine in hypertensive SH patients showed complete reversal of hypertension in 8/17 (47.05%) cases and partial reversal in one (5.88%) and no reversal in 8 cases. One case dropped out during follow-up hence was excluded. Further break up of 8 complete reversal of HT cases included 6 cases exhibiting only diastolic hypertension, one case of systolic hypertension and one case of both systolic and diastolic hypertension. One case of both systolic and diastolic hypertension showed partial reversal of hypertension. **Table-2**

Regarding OH cases, levothyroxine therapy resulted in complete reversal in 18 (62.06%) cases, partial reversal in one (3.45%) case, no reversal in 10 cases and one case having both systolic and diastolic hypertension showed partial reversal (3.45%). Four cases dropped out during follow-up. Breakup showed that replacement therapy in OH patients resulted in reversal of systolic hypertension in all 7 patients (100%), while 10/18 (55.56%) cases of diastolic hypertension and one case having both systolic and diastolic hypertension reverted back to normal blood pressure.

Of 6 OH hypertensive patients on antihypertensive therapy, only in 1 patient there was a reduction in number of antihypertensive drugs from two to one, 2 patients showed complete and 1 patient partial reversal of hypertension with levothyroxine replacement without any modification in doses of antihypertensive agent. One patient dropped out during follow-up. The remaining one patient of mild diastolic hypertension who was initially prescribed only levothyroxine exhibited progression of hypertension in first follow-up hence was prescribed antihypertensive drug to render him normotensive.

Two patients of SH having hypertension were on antihypertensive drugs, of these one case did not turn up for follow-up. In the remaining one patient, replacement therapy with levothyroxine resulted in reduction in the dose of antihypertensive drug leading to reversal of only diastolic blood pressure to normal values but no significant effect on systolic blood pressure.

A decreasing trend in mean values of both systolic and diastolic blood pressure in patients of SH as well as OH following levothyroxine therapy was observed. In cases of SH with hypertension, mean systolic blood pressure at baseline was 138 ± 16 mm Hg which declined to 134 ± 12 mm Hg (P<0.05) at first follow-up and to 132 ± 12 mm Hg (P <0.01) at third follow-up. Mean diastolic blood pressure at baseline was 94 ± 4 mm Hg which declined to 90 ± 6 mm Hg (P <0.001) at first follow-up and to 88 ± 6 mm Hg (P <0.001) at third follow-up. In OH patients with hypertension, replacement with levothyroxine resulted in significant decrease in mean values of both systolic and diastolic hypertension. Mean systolic blood pressure at baseline was 138 ± 10 mm Hg which declined to 134 ± 8 mm Hg (P <0.001) at first follow-up and to 132 ± 8 mm Hg (P <0.001) at third follow-up. Mean diastolic blood pressure at baseline was 93 ± 5 mm Hg which declined to 89 ± 6 mm Hg (P <0.001) at first follow-up and to 88 ± 6 mm Hg (P <0.001) at third follow-up. **Table-3**

Table 1: Incidence of hypertension in hypothyroid patients

Hypothyroid Patients	Systolic Hypertension No. (%)	Diastolic Hypertension No. (%)	Both Systolic and Diastolic Hypertension No. (%)	Total Hypertensive cases No. (%)
SH	4 (7.84)	9 (17.65)	5 (9.80)	18 (35.29)
OH	8 (15.69)	19 (37.25)	6 (11.77)	33 (64.71)
Total	12 (23.53)	28 (54.90)	11 (21.57)	51 (100)

Table 2: Influence of replacement therapy with levothyroxine on follow up of hypertension in hypothyroid patients

Hypothyroid Patients	Systolic Hypertension		Diastolic Hypertension		Both Systolic And Diastolic Hypertension		Total No. of cases	
	SH	OH	SH	OH	SH	OH	SH	OH
1st follow-up	4	8	9	19	5	6	18	33
Reversal at 2nd follow-up	1	3	4	4	1	1	6	8
Reversal at 3rd follow-up	0	4	2	6	0	0	2	10
Partial Reversal	0	0	0	0	1	1	1	1
No reversal	2	0	3	8	3	2	8	10
Dropout	1	1	0	1	0	2	1	4

Table 3: Blood pressure before and after levothyroxine replacement therapy in hypothyroid patients with hypertension

Blood Pressure (mm. Hg)		Before Therapy	Levothyroxine Replacement Therapy			
			First Follow-up		Third Follow-up	
		Mean ± S.D.	Mean ± S.D.	p-value	Mean ± S.D.	p-value
SH	**Systolic**	138 ± 16	134 ± 12	< 0.05	132 ± 12	< 0.01
	Diastolic	94 ± 4	90 ± 6	< 0.001	88 ± 6	< 0.001
OH	**Systolic**	138 ± 10	134 ± 8	< 0.001	132 ± 8	< 0.001
	Diastolic	93 ± 5	89 ± 6	< 0.001	88 ± 6	< 0.001

DISCUSSION

Hypothyroidism is the second most common ailment afflicting patients attending the endocrinology outpatient department. The most common type of hypothyroidism is that caused by primary thyroid gland failure. Basic causes of primary hypothyroidism are auto-immune, silent, postablative, goitrous, athyreotic and non-autoimmune (e.g. Riedel's) and subacute thyroiditis.[2]

The reported prevalence of subclinical hypothyroidism (SH) varying from 4-17% of a normal population.[1] The incidence of hypothyroidism in the present study was found to be 3.83% (SH 1.96% and OH 1.87%). Contrary to our findings, Jung et al[8] reported prevalence of SH 0.64% and OH 0.16% whereas Pirich et al[9] reported the prevalence of newly diagnosed SH as 1.1% and no case of overt hypothyroidism. In the present study, the prevalence of SH was more common compared to OH cases. Our findings are in concurrence with other workers.[8]

A predominance of females (M: F ratio 1:6.5) was noted in hypothyroid patients. Incidence of males and females in SH cases were 3.89% and 47.22% respectively, and in OH 9.44% and 39.44% respectively. In a cross-sectional study the prevalence of SH in males and females were found 4.3% and 15.0% respectively and in OH 2.6% and 8.4%, respectively.[10] These findings are at variance with those of our observations.

With regard to prevalence of hypertension, of 180 patients of hypothyroidism, hypertension was found in 51 (28.33%) patients suggesting that hypertension was fairly common in myxoedema. 33/88 (37.5%) patients of OH and 18/92 (19.57%) patients of SH were hypertensive. Only systolic blood pressure was raised in 12 cases, diastolic in 28 and both systolic and diastolic in 11 cases. A variable incidence of hypertension was observed in cases of myxoedema by different workers in the field. Saito et al[3] found 15% of myxoedema patients to be hypertensive in a series of 477 patients. On the other hand, Anderson et al[11] reported almost 50% persons of endocrinal diseases to be afflicted with hypertension, including myxoedema.

Hypothyroidism is responsible for many effects on the cardiovascular system including hypertension which is a major cause of coronary heart disease. The hypothyroid population is characterized by significant volume changes, initiating a volume dependant low plasma rennin activity as mechanism of blood pressure elevation.[2] Moreover, subclinical or mild hypothyroidism is often associated with adverse cardiovascular risk factors such as high cholesterol together with hypertension, endothelial dysfunction and other atherosclerotic cardiovascular risk factors.[1] Walsh et al[12] found significant relationship between subclinical hypothyroidism and ischemic heart disease, but no relationship between subclinical hypothyroidism and mortality in Australia. Overt hypothyroidism is associated with abnormal hemodynamics resulting in reduced cardiac index and an impaired renal perfusion along with increased morbidity and mortality.[1] Workers in the field also observed that the pattern of cardiovascular abnormalities was similar in subclinical and overt hypothyroidism, suggesting that even lesser degree of thyroid hormone deficiency might affect the cardiovascular system.[5,6] Thus, an increased frequency of hypertension was observed even in patients with subclinical hypothyroidism.[13-15] Conversely others reported no association between hypertension and subclinical hypothyroidism.[16,17]

It was suggested that mild thyroid failure might increase diastolic blood pressure as a result of increased systemic vascular resistance.[4,6] Saito et al[3] in a study of 477 female hypothyroid patients with chronic thyroiditis observed only a raised diastolic blood pressure but not systolic blood pressure. This finding was contrary to our observations since both diastolic and /or systolic blood pressure was raised. Kotsis et al[18] also observed that both systolic and diastolic blood pressures were significantly higher in patients with hypothyroidism compared with volunteers thus concurring with our observations.

In the present study, the number of patients having only diastolic hypertension was comparatively more in both the groups of hypothyroidism (9 out of 18 SH and 19 out of 33 OH), accounting for a total of 54.9% of hypothyroid patients having hypertension. Other workers[3,5,19] also reported a higher incidence of diastolic hypertension in hypothyroid patients thus supporting our observations. Streeten et al[20] observed that induction of hypothyroidism in 40 thyrotoxic patients by ^{131}I significantly increased diastolic blood pressure in 16 (40%) patients. In contrast, Bergus et al[21] found no difference in mean diastolic blood pressure in the euthyroid and hypothyroid groups (80.1 mm Hg vs 78.9 mm Hg, $p = 0.25$) and there was no significant association between having hypertension and level of TSH ($p = 0.33$).

It was reported that in cases of hypothyroidism associated with hypertension, restoration of euthyroidism with levothyroxine therapy usually resulted in a substantial reduction in both systolic and diastolic blood pressure.[7] In the present study, replacement therapy with levothyroxine in SH patients having hypertension caused complete reversal of hypertension in 8/17 (47.05%) cases. Saito et al[3] observed that prolonged and adequate thyroid hormone replacement therapy resulted in

reduction of blood pressure (diastolic) in concurrence with our findings. Other workers in the field in agreement with our findings also observed that there was a tendency of increased diastolic blood pressure even in mild degree of thyroid hormone deficiency and that this abnormality regressed with levothyroxine replacement therapy.[5,6]

It was observed that following replacement therapy with levothyroxine in patients of OH, complete reversal of hypertension resulted in 18 out of 29 (62.06%) cases. Concurring with our views, Richards et al[22] reported that arterial pressure fell significantly following replacement with thyroxine in four out of five patients of hypothyroidism with hypertension. Saito et al[3] also observed that adequate thyroid hormone replacement therapy for an average of 14.8 months in hypothyroid patients with hypertension resulted in a normalization of thyroid function and reduction of blood pressure ($p<0.01$).

Initially eight patients of hypothyroidism (2 SH, 6 OH) were on antihypertensive drugs. There was one dropout each in both the groups. The only patient of SH responded with a reduction in the dose of antihypertensive drugs and partial reversal of hypertension (diastolic blood pressure reverted to normal but no significant effect on systolic blood pressure). Of 5 remaining OH patients, only in 1 patient there was a reduction in number of antihypertensive drugs from two to one, 2 patients showed complete and one patient partial reversal of hypertension without any modification in doses of antihypertensive agents. Remaining one patient of mild diastolic hypertension was initially prescribed only levothyroxine but the case unusually exhibited progression of hypertension in first follow-up hence was prescribed antihypertensive drug to make him normotensive. Owing to very small number of antihypertensive treated cases in the present study, a clear-cut opinion regarding reduction in the dose of antihypertensive drugs or their number cannot be clearly expressed and this aspect needed further investigations.

Streeten et al[20] in their study of 688 hypertensive patients, referred for evaluation and therapy of hypertension, found hypothyroidism in 25 (3.6%) of them. Restoration of normal thyroid status with levothyroxine replacement therapy lowered diastolic blood pressure to <90 mm Hg in 32% of these patients who could be followed up after withdrawal of all antihypertensive drug therapy when euthyroidism had been restored (i.e., 1.2% of the 688 patients).

In the present study a statistically significant decrease in mean values of both systolic and diastolic blood pressure in hypertensive patients of SH was noted when treated with levothyroxine. Monzani et al[23] also reported a decrease in mean systolic BP (117 ± 15 mm Hg vs 112 ± 15 mm Hg) as well as mean diastolic BP (72 ±11 mm Hg vs 69 ± 9 mm Hg), thus supporting our observations.

Similarly in hypertensive patients of OH replacement therapy caused a significant decrease in mean values of systolic as well as diastolic blood pressure. In a study of 30 patients of hypothyroidism with hypertension, levothyroxine therapy caused complete normalization of blood pressure (118/83 +/- 8/3 mm Hg) in 15 patients whereas in remaining 15 patients only a small decrease in blood pressure (151/105 +/- 9/9 mm Hg) was observed[24]. These findings support our observations.

In the present study, five cases (4 OH, 1 SH) were excluded for the purpose of study owing to noncompliance or failure to report. This may be attributed to their careless attitude, a near symptomless affliction of the disease, or due to financial constrains or poor awareness regarding the gravity of the disease.

In conclusion, hypothyroidism whether subclinical or overt, is often accompanied by systolic and/or diastolic hypertension which may cause adverse repercussions on the cardiovascular system. Our findings suggest that early institution of adequate thyroid replacement therapy with levothyroxine for prolonged period may play a pivotal role in reversal of hypertension in majority of cases and may reduce cardiovascular risk factors. Although, it may be emphasized that most studies of subclinical hypothyroidism are observational, and it does not always follow that treatment of SH will reduce the risk of cardiovascular disease and mortality. To demonstrate such a benefit, very large clinical trails with a very long follow-up period are required.

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