Hypothyroidism as a Cause of Hypertension

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SUMMARY To study whether there is an association between hypertension and hypothyroidism, measurements of blood pressure and thyroid function were determined in 477 female patients with chronic thyroiditis. Based on the blood levels of thyroxine (T_4) and thyroid stimulating hormone (TSH), 308 patients were considered euthyroid and 169 were hypothyroid [T_4 = 2.9 ± 0.1 μg/dl and TSH = 105.8 ± 6.8 μU/ml (mean ± SEM)]. Diastolic, but not systolic, blood pressure in hypothyroid patients over 50 years was higher than in euthyroid patients of corresponding age groups. The prevalence of hypertension was higher in hypothyroid patients when hypertension was defined as the systolic and/or diastolic blood pressure above 160/95 mm Hg (14.8% vs 5.5%; $p < 0.01$). Correlations between diastolic, but not systolic, blood pressure and either the blood level of triiodothyronine (T_3) or T_4 was significant ($r = -0.174$, $p < 0.01$, and $r = -0.208$, $p < 0.01$, respectively) when data from both euthyroid and hypothyroid patients were combined. Adequate thyroid hormone replacement therapy for an average 14.8 months in 14 patients resulted in a normalization of thyroid function and a reduction of blood pressure ($p < 0.01$). In four who showed no change in thyroid function due to inadequate replacement therapy, blood pressure remained elevated. These results suggest a close association between hypertension and hypothyroidism.

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KEY WORDS • blood pressure • thyroid deficiency • thyroxine treatment • chronic thyroiditis

HYPOTHYROIDISM is listed as a cause of secondary hypertension in some textbooks of hypertension; however, there appears to be less certainty about the prevalence of hypertension. For example, in Kaplan's *Clinical Hypertension*, the prevalence is reported as 26%,[1] and in Genest's *Hypertension, Physiology and Treatment*, the prevalence is reported as 50%.[2] On the other hand, Skelton and Sonnenblick[3] have reported either low or normal blood pressure in this disorder. This report describes the relation of thyroid function and blood pressure, compares the age-related increase in blood pressure in euthyroid patients with that of hypothyroid patients, and assesses the effect of thyroid hormone replacement therapy on blood pressure in hypertensive hypothyroid patients. The results suggest a high prevalence of hypertension in hypothyroid patients over 50 years old.

Methods

Patient Population

This investigation involved 477 patients with chronic thyroiditis; they ranged in age from 20 to 69 years. They visited Ito Hospital between January 1980 and December 1980 and were seen by one of the authors. The diagnosis of chronic thyroiditis was based on the presence of goiter and the demonstration of circulating thyroid antibodies (microsomal and thyroglobulin). None had previously been treated for hypothyroidism or hypertension.

To assess the degree of thyroid deficiency, these patients were divided according to the levels of serum thyroxine (T_4) and thyroid stimulating hormone (TSH) concentrations. Patients with T_4 levels more than 5 μg/dl (lower limits of normal range) and TSH levels less than 6 μU/ml (upper limits of normal range) were considered euthyroid; those with levels less than 5 μg/dl of T_4 and more than 6 μU/ml of TSH were considered hypothyroid.

Methods

Those with a systolic and/or diastolic blood pressure exceeding 160/95 mm Hg were defined hypertensive. Brachial arterial pressure was measured with a sphygmomanometer after 30 minutes of rest with the patients seated in a quiet room. Serum T_3, T_4, and TSH were determined by radioimmunoassay techniques using kits obtained from Dainabbot Company, Tokyo. The interassay coefficients of variation for T_3, T_4, and TSH were 4.0%, 4.5%, and 5.4%, respectively. Lower limits of sensitivity of radioimmunoassay of TSH were 0.2 μU/ml. Antithyroglobulin and antimicrosomal

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antibodies were determined by hemagglutination, using reagent kits from Fujizoki, Tokyo.[4]

Values are expressed as means ± SEM. Statistical analysis was done by Student's *t* test for paired and unpaired data as appropriate and chi square test. Correlations were calculated by the method of least squares.

Results

Age-Matched Comparisons Between Euthyroid and Hypothyroid Patients

Table 1 presents the clinical characteristics of patients. Euthyroid patients had higher serum T_4 and T_3 and lower TSH values than hypothyroid patients. Both groups were similar in weight, height, and body mass index (BMI). Table 2 shows the number of patients and prevalence of hypertension by age. Twenty-five of 169 patients (14.8%) in hypothyroid patients and 17 of 308 (5.5%) in euthyroid patients had hypertension.

For both euthyroid and hypothyroid patients, blood pressure increased with age (fig. 1). Nevertheless, hypothyroid patients had significantly higher diastolic blood pressure than euthyroid patients in the 5th and 6th decades. Heart rate in euthyroid patients was higher than in hypothyroid patients; however, the difference did not reach statistical significance in the 40- to 49-year and 60- to 69-year groups (fig. 2).

Correlations

Diastolic, but not systolic, blood pressure correlated significantly with T_4 and T_3 in hypothyroid patients ($r = -0.202$, $p < 0.01$, and $r = -0.229$, $p < 0.01$, respectively). There was no significant correlation between diastolic blood pressure and TSH in this group. No significant correlations were observed between blood pressure and either T_4, T_3, or TSH in euthyroid patients. Correlations between diastolic blood pressure and either T_3 or T_4 were significant ($r = -0.174$, $p < 0.01$, and $r = -0.208$, $p < 0.01$, respectively) when data from both euthyroid and hypothyroid patients were combined.

TABLE 1 *Clinical Characteristics*

	Euthyroid (n = 308)	Hypothyroid (n = 169)	Significance
Weight (kg)	51.1 ± 1.2	52.9 ± 1.0	ns
Height (cm)	152.1 ± 0.8	153.0 ± 0.9	ns
BMI	22.1 ± 0.5	22.6 ± 0.4	ns
T_4 (μg/dl)	8.7 ± 0.1	2.9 ± 0.1	<0.001
T_3 (ng/dl)	125.7 ± 1.9	77.1 ± 2.7	<0.001
TSH (μU/ml)	2.9 ± 0.1	105.8 ± 6.8	<0.001

Values are means ± SEM; analysis of differences was based on *t* test.

BMI = body mass index; T_4 = thyroxine; T_3 = triiodothyronine; TSH = thyroid-stimulating hormone.

TABLE 2. *Number of Patients and Prevalence of Hypertension by Age*

Age (yr)	Patients with hypertension		Significance*
	Euthyroid	Hypothyroid	
20–29	0/55 (0%)	0/34 (0%)	ns
30–39	1/51 (2.0%)	1/33 (3.0%)	ns
40–49	5/73 (6.8%)	5/37 (13.5%)	ns
50–59	6/88 (6.8%)	12/41 (29.3%)	<0.01
60–69	5/41 (12 2%)	7/24 (29.2%)	ns
Total	17/308 (5 5%)	25/169 (14.8%)	<0 01

*Determined by the chi square test

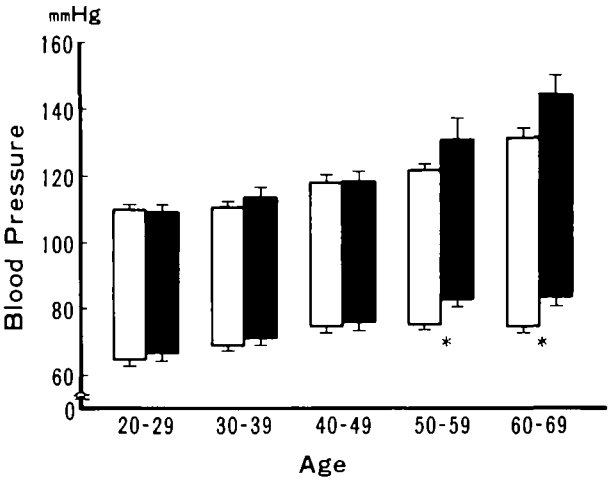

FIGURE 1. *Systolic and diastolic blood pressure in euthyroid (open bar) and hypothyroid (black bar) patients by age. Means ± SEM are given. *p < 0.01; statistical analysis between two groups was based on unpaired t test.*

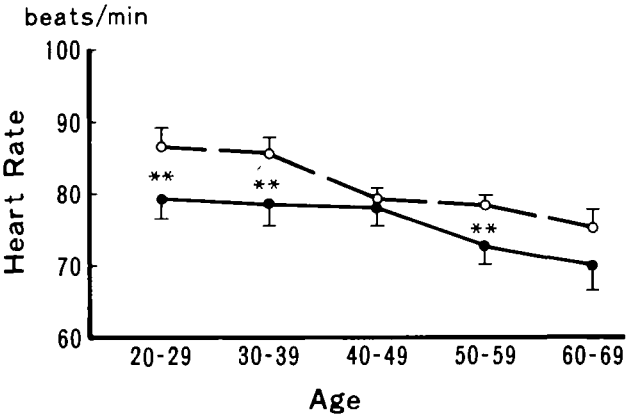

FIGURE 2. *Heart rate in euthyroid (open circle) and hypothyroid (black circle) patients by age. Means ± SEM are given. **p < 0.05; statistical analysis between two groups was based on unpaired t test.*

TABLE 3. *Response of Blood Pressure and Thyroid Function Test to T_4 Replacement Therapy*

	Group 1		Group 2	
	Pre	Post	Pre	Post
Systolic BP (mm Hg)	157.0±5.0	143.0±2.9*	160.8±18.1	161.6±24 8
Diastolic BP (mm Hg)	99.0±6.5	90.5±3.3*	100.0±3 7	99.5±4.7
T_3 (ng/dl)	63 6±5 7	112.0±6.8*	75.0±22.9	113 3±27.7
T_4 (μg/dl)	2.5±0.4	10.3±1.4*	3.2±1.1	6.1±1.4
TSH (μU/ml)	99.2±22.4	4.8±1.1*	125.5±76.1	56.1±22.4

Group 1 = adequately treated, n = 14; Group 2 = inadequately treated, n = 4
*$p < 0.01$ compared to Pre in each group, by paired t test.

Blood Pressure Response to Thyroid Hormone Replacement

A follow-up study was made of 18 hypertensive hypothyroid patients aged 35 to 69 years. Blood pressure and thyroid function tests were followed for 14.5 ± 2.0 months.

In 14 patients (Group 1) who received sodium-L-thyroxine, 100 to 150 μg/daily, treatment suppressed TSH and increased serum T_3 and T_4 into normal range and was, therefore, considered adequate. All except one exhibited significant reductions of blood pressure. In four patients (Group 2) who did not receive adequate amount of sodium-L-thyroxine due to poor compliance, blood pressure and thyroid function tests remained unchanged (table 3).

Discussion

Although it has been shown that hypertension accompanies hypothyroidism, its prevalence remains to be established since wide-ranging rates from 0 to 50% have been reported.[1-3] Furthermore, few reports compared the age-related increase of blood pressure in hypothyroid patients with that of euthyroid patients.

In the present study, only female subjects were included in order to avoid sex-related factors that could influence blood pressure. Another important factor that could influence the blood pressure is relative adiposity.[5, 6] In the present study, there were no significant differences in weight, height, and body mass index between euthyroid and hypothyroid patients. Thus, the difference in relative adiposity may be excluded as a factor that could influence the results of this study.

In subjects over 50 years old, diastolic blood pressure of hypothyroid patients was significantly higher than that of euthyroid patients whose age-related change in blood pressure was similar to that of normal subjects in an epidemiological study in Japan.[7] The finding suggests that the hypothyroid state accelerates the age-related increases in blood pressure. When the hypertension is defined as a blood pressure above 160/95 mm Hg, the prevalence of hypertension was significantly higher in hypothyroid patients than euthyroid patients.

The prevalence of hypertension in hypothyroid patients demonstrated in this study is not in complete agreement with that reported by Attarian.[8] However, the mean age of his subjects was greater than that of this study. The prevalence of hypertension in the subjects over 50 years old in the present study was approximately 30% and was similar to that of Attarian. Endo and coworkers[9] reported that the prevalence of hypertension was higher in slightly hypothyroid, but not severely hypothyroid, patients than in normal subjects. In the present study, severity of thyroid deficiency was considered slight to moderate, since their average T_4 and T_3 levels were 2.9 ± 0.1 μg/dl and 77.1 ± 2.7 ng/dl, respectively, and none of them showed severe symptoms of hypothyroidism. Furthermore, significant correlations between diastolic blood pressure and either T_4 or T_3 suggest that thyroid hormone deficiency contributes to increase in blood pressure when it is slight to moderate.

The mechanism of increased blood pressure in hypothyroidism is not known; however, an acceleration of structural change of vascular tissue by thyroid hormone deficiency may be a local factor in causing a higher total peripheral resistance.[10] Furthermore, alteration of autonomic nervous function by thyroid hormone deficiency could cause hemodynamic changes. Increases in plasma norepinephrine concentration, mainly due to increased secretion rate, rather than decreased metabolism of norepinephrine have been demonstrated in hypothyroid patients.[11] High serum prolactin and TSH concentration, seen in patients with hypothyroidism, suggest a reduced dopaminergic activity in central nervous system[12, 13] that could contribute to the development of hypertension by enhancing norepinephrine release.[14] Normalization of central dopaminergic activity by thyroid hormone replacement therapy could be one of the factors in reducing blood pressure in the hypertensive hypothyroid patients.

The recent demonstrations that hypertensive subjects have a higher prevalence of high circulating TSH than normotensive subjects[15] and that spontaneously hypertensive rats have higher serum TSH[16, 17] have raised some speculation that primary hypertension and hypothyroid state might be intimately associated. Data

on this particular aspect are fragmentary and must await further studies. However, because of high prevalence of hypertension among hypothyroid patients over 50 years old, thyroid hormone deficiency should merit some consideration in the initial evaluation of the hypertensive patients.

In summary, our studies have confirmed that hypertension is more often associated with hypothyroidism than euthyroidism in patients over 50 years old, and that blood pressure is often reduced in response to adequate thyroid hormone replacement therapy alone. As a mechanism of this hypertension, we suggest that the reduced dopaminergic activity resulting from thyroid hormone deficiency leads to enhanced sympathetic nervous tone, which could be responsible for the hypertensive state. However, other local factors could be involved. The exact mechanism(s) leading to hypertension remains to be determined.

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