Effects of Thyroid Function on Blood Pressure
Recognition of Hypothyroid Hypertension

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SUMMARY Hypothyroidism has been known to be associated, at times, with diastolic hypertension. We have found in 40 thyrotoxic patients that the induction of hypothyroidism by radioiodine therapy significantly increased diastolic blood pressure, raising it above 90 mm Hg in 16 (40%) of the patients. Restoration of euthyroidism with thyroxine administration significantly reduced the systolic and diastolic blood pressures in these patients, with a fall in diastolic pressure below 90 mm Hg in nine of 16 patients. The prevalence of hypothyroidism was determined by measurements of serum thyroxine and thyrotropin concentrations in 688 consecutive hypertensive patients, referred for evaluation and therapy of their hypertension. Hypothyroidism was found in 25 (3.6%) of the patients. Restoration of normal serum thyroxine and thyrotropin levels with thyroid hormone replacement therapy lowered diastolic blood pressure to levels below 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). It is concluded that diastolic hypertension resulting from hypothyroidism is a relatively common disorder, present in 1.2% of our referred hypertensive patients, that should be sought and treated. (Hypertension 11: 78-83, 1988)

KEY WORDS • hypothyroid hypertension • endocrine hypertension • thyroid in hypertension

HYPERTHYROIDISM is usually associated with peripheral vasodilatation and reduction of the diastolic blood pressure (BP) and sometimes with systolic hypertension, while hypothyroidism may be accompanied by diastolic hypertension, as many clinicians are aware. Elevation of the diastolic BP was found to be common in patients with hypothyroidism1 and has been reported in small groups of patients with hypothyroidism and myxedema by several investigators,2-6 who have all found a fall in diastolic BP when the hypothyroidism was corrected with thyroid replacement therapy. The latter observations were preceded by a report that desiccated thyroid administration lowered the BP to normal levels in 14% of 334 patients with essential hypertension, at a time (in 1950) when virtually no effective forms of antihypertensive therapy were available.7 Similar findings were reported by Fuller et al.2 However, in a comparison of BP measurements in 80 hypothyroid patients and 73 euthyroid subjects, Endo et al.8 found no evidence that hypothyroidism predisposed to hypertension. Apart from this negative study, there have been no recent attempts to determine the frequency with which hypertension may be associated with and caused by hypothyroidism, the treatment of which will restore the BP to normal. We have sought to obtain this information 1) by studying the BP responses of a series of patients with thyrotoxicosis to therapy with radioiodine as they became euthyroid and, frequently, hypothyroid and 2) by measuring the prevalence of hypothyroidism in 688 consecutive, referred patients with hypertension and, in those found to be hypothyroid, by determining the effect of thyroid replacement therapy on the BP. Some of these data have been published previously in abstract form.9

Patients and Methods
Serial BP measurements were made with an aneroid sphygmomanometer in a series of 40 patients who were referred for hyperthyroidism. The patients were aged 30 to 65 years, of both sexes (35 women, 5 men), and almost all were of normal weight when first seen.

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BP was measured in the sitting posture, at each office visit, before treatment with iodine-131 (80 μCi/g of estimated thyroid weight); 3 to 6 months later when euthyroidism had been restored; during the subsequent development of hypothyroidism, which commonly follows radioiodine treatment; and after the restoration of euthyroidism by replacement therapy with sufficient L-thyroxine or desiccated thyroid to restore serum thyroid stimulating hormone (TSH) concentrations to normal. Measurements of serum T4 and TSH levels were made by radioimmunoassay at each visit.

In 688 consecutive, untreated patients referred for study and management of their hypertension, we measured BP in the recumbent and standing postures with an aneroid sphygmomanometer; serum T4, TSH, and electrolyte concentrations, as well as plasma renin activity (PRA), after furosemide, 40 mg i.v., and standing for 2 hours; BP response to the angiotensin II antagonist saralasin; and plasma aldosterone concentration after an intravenous infusion of 2 L of 0.9% NaCl given over 3.5 hours. The patients varied in age from 15 to 70 years, were evenly divided between female and male (55:45) patients, and had a mean body weight of 79.6 kg. Only in three of the five patients whose serum TSH exceeded 30 μIU/ml was the diagnosis of hypothyroidism suspected on clinical grounds. Female patients predominated (75:25) among those patients who were found to be hypothyroid. Mean body weight in the hypothyroid patients was 81.5 ± 2.9 kg, and mean age was 49.8 ± 2.5 years. Patients who were found to be hypothyroid were given L-thyroxine in addition to their usual antihypertensive drugs in increasing doses until serum T4 and TSH concentrations were restored to normal. When this had been accomplished, their hypotensive medications were tapered and stopped to determine whether the BP would remain in the normal range during treatment with thyroid replacement only.

All of these studies were approved in advance by the Institutional Review Board for the Protection of Human Subjects at the SUNY Health Science Center (Syracuse, NY, USA).

Results

Figure 1 shows the results of the systolic and diastolic BP measurements in the 40 patients with hyperthyroidism. Before radioiodine therapy, eight of the patients had systolic hypertension and five had diastolic pressures above 90 mm Hg; the mean ± SEM values for the 40 patients were 138.2 ± 3.2/77.7 ± 2.0 mm Hg. When they became euthyroid and remained below 90 mm Hg, the subsequent fall in serum T4 concentration to hypothyroid levels was associated with a change in mean BP to 141.4 ± 4.6/88.4 ± 2.4 mm Hg. When they were hypothyroid, 16 of the 40 patients had diastolic BPs above 90 mm Hg. Restoration of euthyroidism (T4 and TSH both within normal limits) by replacement therapy, reduced the diastolic BP below 90 mm Hg in all except seven of the patients (five of whom also had had diastolic hypertension when thyrotoxic), while the BP in the entire group averaged 130.6 ± 1.9/80.8 ± 1.9 mm Hg. The changes in diastolic BP from the thyrotoxic to the hypothyroid and euthyroid states were highly significant by analysis of variance (p < 0.0001). The changes in systolic BP were not significant. No clinical or laboratory differences were found between the patients whose diastolic BP rose above 90 mm Hg during hypothyroidism and those whose diastolic BP remained below 90 mm Hg. However, there were significant correlations between the diastolic BPs during hyperthyroidism and hypothyroidism (r = +0.576, p < 0.001), during hyperthyroidism and euthyroidism (r = +0.476, p < 0.005), and during hypothyroidism and euthyroidism (r = +0.653, p < 0.001).

A computer printout of the serum T4 and TSH concentrations in the 688 untreated hypertensive patients is shown in Figure 2. It is evident that serum T4 was elevated (>12 μg/dl) in 26 (3.8%) of the patients, while hypothyroidism (serum T4 <5 μg/dl or serum TSH >7 μIU/ml, or both) was present in 25 (3.6%) of the patients. Only three of these patients had clinical features suggesting hypothyroidism.

Figure 3 shows the results of various functional measurements in the 25 hypertensive patients who were found to have hypothyroidism. Plasma renin activity, stimulated by furosemide diuresis and orthostasis, was subnormal (below 1.7 ng/ml/hr) in 13 of 25 (52%) patients. Plasma aldosterone fell into the normal range (1.7–8.5 ng/dl) in all but one of the 22 patients in whom it was measured after the 2-L saline infusion. Intravenous infusion of saralasin, at 0.05 to 20 μg/kg/min, lowered the diastolic BP more than normally (i.e., by >8 mm Hg) in three, raised it to some extent in 17 patients, and raised diastolic BP by more than 8 mm Hg in six of these 17 patients. Cardiac index, measured in two patients, was high-normal in one and low-normal in the other patient, while systemic vascular resistance was elevated in both patients studied.

Follow-up was incomplete in five of the hypothyroid patients because of death (one), loss to follow-up (two), and departure of the patient from this area (two). Figure 4 shows BP responses to the restoration of euthyroidism in the remaining 20 hypothyroid patients. In eight, diastolic BP fell below 90 mm Hg when they became euthyroid and remained below 90 mm Hg when all antihypertensive medications had been stopped for at least 6 months. In the other 12 patients diastolic BP remained above 90 mm Hg when euthyroidism had been restored unless antihypertensive drugs were administered. Four of the patients in this group had severe renal insufficiency, with one of the four requiring chronic hemodialysis. Female patients predominated both in those whose BP fell to normal levels on thyroxine therapy alone (6 female, 2 male patients) and in those who continued to require other antihypertensive therapy after they had become euthyroid (9 female, 3 male patients); both groups reflected the preponderance of women among hypo-
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FIGURE 1. Systolic and diastolic BP readings related to serum thyroxine (T4) or protein-bound iodine (PBI) concentrations in 40 patients during their conversion from thyrotoxicosis (T4 > 12 µg/dl) to euthyroidism (T4 = 5–12 µg/dl) to hypothyroidism (T4 < 5 µg/dl) and finally to euthyroidism during T4 replacement therapy. Diastolic BP was above 90 mm Hg in five patients during thyrotoxicosis, in 16 patients during hypothyroidism, and in seven patients during subsequent euthyroidism restored by T4 replacement therapy.

Discussion

It is evident from this study that diastolic BP rose significantly during the change from hyperthyroidism to hypothyroidism and fell significantly when euthyroidism was restored in the 40 originally thyrotoxic patients. These observations confirm the similar findings described by Davis and Davis in some of the elderly thyrotoxic patients whose clinical responses to radioactive iodine therapy they reported. No less than 40% of our patients had diastolic BPs over 90 mm Hg when they were hypothyroid, and in most of these the blood pressure fell below 90 mm Hg after adequate replacement therapy. These data certainly substantiate the theoretical possibility that some patients who are seen with hypertension might have unrecognized hypothyroidism and could be restored to normotension with thyroxine replacement therapy alone.

The serum T4 and TSH measurements in the 688 hypertensive patients revealed the presence of unrecognized hypothyroidism in 3.6%. Although serum T4 concentration was normal in several of these patients, the elevation of serum TSH levels was assumed to indicate the presence of primary hypothyroidism, in accordance with current views. Among the hypothyroid patients, there was a higher prevalence (52%) of low renin hypertension (associated with subnormal stimulated PRA levels and an agonistic BP response to saralasin) than in euthyroid hypertensive patients of whom 30% had low PRA levels. The suppressed level of PRA did not result from autonomously and unsuppressibly elevated plasma aldosterone concentrations, except in one patient, who did not have evidence of an adrenal adenoma by computed tomographic scanning. The hemodynamic measurements in two of these patients disclosed elevation of the systemic vascular resistance, as is found in most patients with sustained hypertension.

It was of interest to find that in no less than eight patients with unrecognized hypothyroidism, or 1.2% of the 688 patients studied, therapeutic restoration of euthyroidism was associated with a fall in diastolic BP below 90 mm Hg. It is possible that the fall in BP...
HYPOTHYROIDISM CAUSING HYPERTENSION/Streeten et al. 81

FIGURE 2. Serum thyroxine and thyrotropin (TSH) concentrations in 688 untreated hypertensive patients referred for refractoriness to therapy. In 25 patients (large dots) hypothyroidism was evident from subnormal serum thyroxine (in 11) or elevated serum TSH (in 19) concentrations or both.

represented a placebo response, though the lack of an adequate reduction of BP during treatment given before the initiation of T4 replacement therapy would argue against that possibility. Thus, in these individuals, 1.2% of the 688 patients studied, it is reasonable to attribute their hypertension to the demonstrated hypothyroidism and it was possible to control the hypertension with thyroxine alone, without the variety of antihypertensive drugs that they had been given before cessation of the therapy for the diagnostic studies. The hypothyroid patients whose diastolic BP fell below 90 mm Hg on L-thyroxine therapy alone were younger than those who continued to require other antihypertensive therapy after becoming euthyroid. Our recent observations in patients with primary aldosteronism and renal arterial stenosis (D. H. P. Streeten, G. H. Anderson, Jr., S. Wagner, unpublished observations, 1987) have confirmed the general principle that hypertension in older persons frequently persists when the initiating cause has been removed. It is possible, therefore, that if hypothyroidism had been discovered and treated at an earlier age, more of our patients would have been responsive to T4 alone.

Although the prevalence of hypothyroidism in our hypertensive patients cannot be taken to indicate its prevalence in the entire hypertensive population, it is likely that a large number of hypertensive patients are being given a vast array of modern antihypertensive drugs instead of the one hormone, T4, which they really need both to correct their hypertension and to overcome their hypothyroidism. Since hypothyroidism is mild and usually not clinically recognizable and since

FIGURE 3. Measurements of PRA (after furosemide and standing for 2 hours), plasma aldosterone concentration (after 2 L of 0.9% NaCl i.v.), change in diastolic BP during saralasin infusion, cardiac index, and systemic vascular resistance in 25 hypertensive patients with hypothyroidism. Normal ranges are shown by crosshatching. Data from patients who subsequently became normotensive during thyroxine (T4) therapy are shown with circles, and the findings in those whose hypertension persisted during subsequent euthyroidism are shown with squares.
FIGURE 4. Measurements of serum thyrotropin (TSH) and thyroxine (T4) concentrations and BP in 20 patients during hypothyroidism (●) and therapeutically restored euthyroidism (○). Restoration of euthyroidism was associated with a fall in diastolic BP to or below 90 mm Hg in eight of the 20 patients.

most of these patients can be diagnosed with a serum TSH measurement alone, the desirability of performing this determination routinely on hypertensive patients is worthy of consideration.

The mechanism of hypertension in patients with hypothyroidism is not known. Our finding of low stimulated PRA levels in 52% of these patients confirms previous reports of low PRA levels in patients with hypothyroid hypertension.\(^5,15\) Thyroidectomy reduced PRA in rats.\(^16\) These results might indicate that fluid retention and extracellular fluid volume expansion in hypothyroidism\(^17,18\) might be the mechanism of the hypertension. There is also evidence for a potential role of norepinephrine in the hypertension of patients with hypothyroidism, both urinary excretion\(^19\) and plasma concentration of norepinephrine\(^30\) being elevated in hypothyroid patients. However, interpretation of the relevance of these findings to the pathogenesis of hypertension is complicated by the observations of Schneckloth et al.,\(^21\) who found reduction of the pressor responsiveness to norepinephrine in a patient with myxedema and excessive norepinephrine responsiveness in four thyrotoxic patients.

The effects of changes in thyroid function on the BP have been studied in spontaneously hypertensive rats (SHR). Fregly\(^22\) reported that SHR had lower I\(^3\)I-uptake by the thyroid gland than normotensive control animals. However, thyroidectomy or administration of propylthiouracil prevented the expected rise in BP, both in renal hypertension\(^23\) and in NaCl-induced hypertension in rats.\(^24\) Serum T\(_4\) concentrations are lower in the prehypertensive stage of SHR, but thyroidectomy at this stage prevents the later development of hypertension.\(^25\) These observations in SHR were made in relation to the systolic BP. If they have any bearing on the pathogenesis of hypertension in humans, they may be more related to isolated systolic hypertension, such as that seen in 20% of our thyrotoxic patients, than to diastolic hypertension.

References

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