

Hypothyroidism as a Potential Risk Factor in Hypertensive Patients

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Abstract: There have been previous studies examining the association between thyroid dysfunction and cardiovascular disease. Hypothyroidism is related to an increased risk of functional cardiovascular abnormalities, particularly for hypertension. The aim was to characterize the prevalence of hypothyroidism as a risk factor for arterial hypertension in a community-based study in San Luis, Argentina. Cross-sectional, retrospective and descriptive studies were designed. A total of 1,023 individuals were recorded at a cardiologic center (2006- 2008). Data abstracted from clinical history included: age, sex, hypertension (HTA >140/90 mm Hg), and serum thyroid function tests: TSH, T₄ and T₃. The investigation involved 698 patients with HTA (74.2% women), 367 with hypothyroidism (81.5% women) and 247 with hypothyroidism-HTA (79,8% women). Ages ranged from 22 to 92 years (mean: 49.9± 11.9) and mean weight 84.3±17.0 kg. Age was positively correlated with body weight ($r=+0.312$, $P=0.003$). TSH mean: 7.67±1.6 μ IU/ml (Men: 6.28±1.2 μ IU/ml, Women: 7.92±2.1 μ IU/ml). The mean systolic (SBP) and diastolic blood pressure (DBP) were 160.8±25.4 mm Hg and 98.8±13.9 mm Hg, respectively. Increasing SBP-DBP for range of TSH was studied. The positive association between TSH and SBP ($r:+0.155$, $P=0.042$) were found. The association between age (four categories) versus SBP in hypothyroidism patients ($r:+0.267$, $P=0.0001$) and the highest percentage was in the age range 51-60 years. DBP was also positively associated with age ($r:+0.200$, $P=0.0001$), highest percentage in age range 41-50 years. There was an important increase in SBP (160.75±19.39-175.43± 21.00 mmHg) and TSH (3.71±2.05-12.06±9.23 μ UI/mL) in hypothyroid patients by age. DBP was highest in the 4th decade (104.70±11.87 mmHg). The positive association between TSH hypothyroidism-HTA and age were found ($r:+0.353$, $P=0.0001$). Serum T₄ (7.78±2.40-6.75±2.15 μ gr/dL) and T₃ (1.24±0.35-0.88±0.26 ng/mL) decreased with age. High prevalence of hypothyroidism in our hypertensive patients was detected (20.8% and 5.6% subclinical). Decrease of serum T₄ and T₃ suggest the lack of blood pressure regulation which could be responsible for the hypertensive state. We found a positive association between TSH and SBP that could have implications for cardiovascular health. These findings indicate that hypothyroidism may be an important predictor of higher mean SBP. In conclusion, in these population patients we found a close association between hypertension and hypothyroidism.

Keywords: hypertension, hypothyroidism, blood pressure, thyroid hormones

Introduction

The cardiovascular system is sensitive to thyroid hormone action and, therefore, the thyroid dysfunction can produce dramatic cardiovascular effects [1]. It is known that hypothyroidism leads to increased vascular resistance, greater arterial wall thickness and endothelial dysfunction [2-4]. The balance of multiple factors depend of the thyroid hormones produced, an abnormal amount could modify the mean blood pressure [1].

Disorders of the thyroid gland can worsen old cardiac symptoms or cause new ones, and can accelerate the underlying heart problem [5]. Thyroid dysfunction has both short-term and long-term cardiovascular consequences [6]. In almost all cases these

cardiovascular changes are reversible when the underlying thyroid disorder is recognized and treated.

Hypothyroidism induces several metabolic changes that allow understanding some physiopathological mechanisms [7]. Prior retrospective studies have suggested an association between thyroid dysfunction and the diagnosis or treatment of hypertension [8], and several case reports have described patients who received diagnoses of both hypertension and thyroid disease [9].

While hypothyroidism is identified as a cause of diastolic hypertension in scientific textbooks and review articles [10-12], others research suggests controversial opinions [8,13-15]. Because hypertension and hypothyroidism are both common



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in the elderly, we would expect to find hypertension and hypothyroidism frequently coexisting even if they are not directly associated. Alternatively, because of the substantial prevalence of hypothyroidism in hypertensive patients an association would be clinically important. We hypothesised that if hypertension and hypothyroidism were related in this population, then we should find a prevalence of hypothyroidism in patients with hypertension. Additionally, if these two conditions were related we would find a positive relationship between systolic and diastolic blood pressures (SBP, DBP) and the levels of thyroid stimulating hormone (TSH) in these patients. The purpose of our work was to characterize the prevalence of hypothyroidism as a risk factor for arterial hypertension in an adult community-based study in San Luis, Argentina.

Materials and Methods

The study population consisted of 1,023 individuals from the Cardiologic Center at San Luis (Argentina) between 2006 and 2008. The studied individuals included in the analysis had 22 year of age or older, and the weight was also recorded. All patients with a complete history and physical examination along with a screening lab panel which includes a TSH, T₃ and T₄ levels on their clinic visit were registered. Study subjects were selected on the basis of the presence of hypothyroidism defined as a single elevated serum TSH level (>5 µU/ml) and the subclinical hypothyroidism has also been estimated from clinical history. These patients had been treated before with antihypertensive treatment, but had been never received drugs for hypothyroidism.

Fasting blood samples were obtained by venepuncture between 07:00–09:00 h from each individual. Analysis of serum TSH concentration was carried out of the population in study. In addition, TSH was measured in samples of men and women.

All participants underwent blood pressure monitoring. After time rest, the arterial pressure from each individual was measured using a standard mercury sphygmomanometer at upper right and left arm, then the mean value was calculated.

The VII Joint National Committee (JNC-7) defined the hypertension as systolic blood pressure (SBP) higher than 140 mmHg and/or diastolic blood pressure (DBP) higher than 90 mmHg.

Serum TSH concentration was analysed using IFMA-MEIA hTSH Ultra (sensitivity 0.01 µUI/ml and total analytical variation < 5%). The reference range for TSH was defined as 0.47–5.01 µUI/ml. T₄ was determined using IFMA-FPIA (reference range: 4.5–12.0 µg/dl) and T₃ by IFMA-MEIA (reference range: 0.76–1.42 ng/ml). The prevalence of hypothyroidism has been estimated from highly sensitive thyroid

hormones assays and clinical history.

The data were analysed using the Statistical Package for the Social Sciences (SPSS), version 17.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistical, frequencies, correlation coefficients, with corresponding 95% confidence intervals (CI), Chi – square test with Yates' continuity correction or chi – square for linear association were used. Differences among groups were evaluated using One-way Analysis of Variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test (Statistical Package GraphPad, version 3.02, San Diego, CA, USA). Means ± standard deviation were calculated and a probability of less than 0.05 was assumed to be significant.

Results

Retrospective record review of 1,023 individuals (75.5% women, 24.5% men) seen in 2006–2008 at a single institution, a Cardiologic Center of San Luis (Argentina). The studied individuals included in the analysis 698 (68.2%) had hypertension (74.2% women, 25.8% men), 35.8 % had hypothyroidism (81.5% women, 18.5% men) and 24.14% hypothyroidism-HTA (79,8 % women, 20,2 % men). The characteristics of the studied population are shown in Table I. We included patients who did not have a previous history of treatment thyroid disease.

Table I. The baseline characteristics of the studied population

	Total	Men	Women
Patients	1023	251	772
HTA Patients	698	180	518
Hypothyroidism	367	68	299
Hypothy-HTA	247	50	197
Age (years)	49.9±11.9	43.77±9.8	51.46±11.8
Weight (Kg)	84.3±17.0	96.92±17.5	78.36±16.5
PAS (mm Hg)	160.8± 25.4	156.2±17.4	161.2±26.6
PAD(mm Hg)	98.8± 3.8	97.4±11.3	98.5±14.7
TSH (µIU/ml)	7.67±1.6	5.35± 1.2	9.62± 2.1

Age and weight frequency distribution of hypothyroidism patients is represented by histogram (Fig. 1 A, B). The person whose age falls in the maximum was 92 years and the minimum age 22 years. The mean age was 49.9±11.9 years. The mean weight was 84.3±17.0 Kg. We have assumed a uniform distribution of data in the both range of age and weight studied.

The current study suggests that high percentage of our population studied had hypertension and hypothyroid pathology, with prevalent percentage of adult females. Women are disproportionately impacted by hypertension and concomitant hypothyroid disease. Although these disadvantages by gender could be explain for some biological basis,

such as, postmenopausal and differences in sex-specific life expectancy [16].

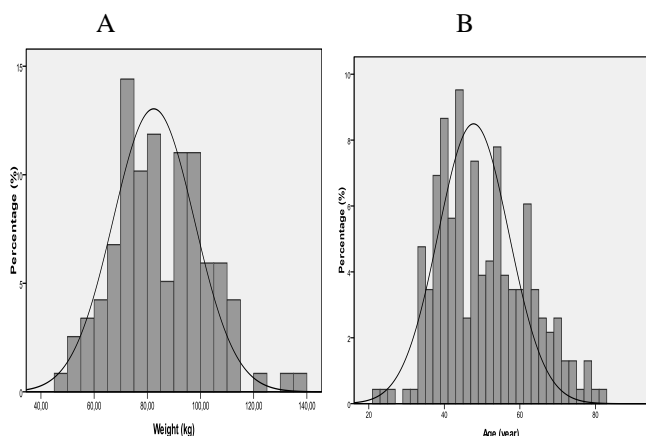


Fig. 1 Weight and age frequency distribution of adult hypothyroid - HTA studied patients. A) Weight, mean \pm SD: 84.3 \pm 17.0 kg. B) Age, mean \pm SD: 49.9 \pm 11.9 years.

Body weight was significantly higher in patients with hypothyroidism. Age was positively correlated with body weight ($r = +0.312$, $P = 0.003$).

At the present time, a sensitive and specific assay of thyroid function exists to establish a diagnosis of thyroid disease. TSH assay was used to establish a diagnosis of hypothyroidism. TSH mean: 7.67 μ IU/mL (Men: 6.28 μ IU/mL, Women: 7.92 μ IU/mL). The mean of TSH concentration was in hypothyroid-hypertensive women higher than men, above of reference range. Similarly, current reports estimate that it affects of the adult female population and a smaller percentage of adult males.

The prevalence of elevated TSH levels (normal range: 0.47-5.01 μ IU/mL) in this population was 20.8% and the prevalence of subclinical hypothyroidism was 5.6%. TSH was positively associated with age ($r: +0.284$, $P = 0.001$). The mean SBP was 160.8 \pm 25.4 mm Hg and the mean DBP was 98.8 \pm 13.9 mm Hg.

Table III. Thyroid hormones, systolic and diastolic blood pressure in relation to hypothyroidism-hypertensive patients' age in years

Age	TSH (μ IU/mL)	T ₄ (μ g/dL)	T ₃ (ng/mL)	SBP (mm Hg)	DBP (mm Hg)
<40	3.71 \pm 2.05	7.78 \pm 2.40	1.24 \pm 0.35	160.75 \pm 19.39	96.86 \pm 14.90
41-50	5.65 \pm 4.54	6.83 \pm 2.65	1.13 \pm 0.24	163.55 \pm 20.55	104.70 \pm 11.87
51-60	11.66 \pm 5.65	6.86 \pm 2.74	0.99 \pm 0.40	165.68 \pm 18.75	99.57 \pm 14.80
>60	12.06 \pm 9.23	6.75 \pm 2.15	0.88 \pm 0.26	175.43 \pm 21.00	103.33 \pm 15.05

TSH levels vary with age, increased markedly in the age from 40 years to >60. Mean plasma TSH was

We investigated associations of hypothyroidism with SBP and DBP in hypertensive subjects. The main outcome measures were mean SBP and DBP (>140/90 mm Hg or current or previous use of antihypertensive medication), according to categories of TSH (Table II).

Table II. Systolic and diastolic blood pressure for range of TSH

TSH (μ IU/ml)	SBP (mm Hg)	DBP (mm Hg)
0.01–0.46	158.23 \pm 4.39	94.70 \pm 3.33
0.47–1.49	158.75 \pm 7.18	98.75 \pm 2.26
1.5–2.49	159.25 \pm 2.75	99.44 \pm 1.74
2.50–5.01	166.76 \pm 3.10	101.23 \pm 1.43
>5.01	166.03 \pm 3.59	97.92 \pm 1.50

We calculated mean systolic and diastolic blood pressure for range of TSH [0.01–0.46, 0.47- 1.49, 1.50–2.49, 2.50–5.01, > 5.02 μ IU/ml]. We found an increase in SBP and DBP with increasing concentration of TSH.

The association between TSH divided in five categories versus SBP and DBP indicate that increase of TSH is corresponding to higher blood pressure in hypothyroid-hypertensive patients.

We also analysed the association between TSH and blood pressure. TSH was positively associated with systolic blood pressure ($r: +0.155$, $P = 0.042$) and no positive association with DBP in hypothyroidism-hypertensive patients were found.

We stratified in Table III the thyroid function test of TSH, T₄ and T₃, SBP and DBP in relation to hypothyroidism-hypertensive patients' age in years (<40, 41-50, 51-60, >60). Correlations analysis was performed considering associations of mean blood pressure and thyroid hormones parameters with age.

higher than reference values. The association between TSH versus four group of age indicate that increase

of TSH is corresponding to higher age ($r=+0.353$, $P=0.0001$). In addition, TSH levels were positively correlated with SBP ($r= +0.228$, $P= 0.002$). There was no significant correlation between DBP and TSH in the hypothyroid-hypertensive group.

Mean levels of T₄ and T₃ hormones were within the normal range. There were no relevant changes in T₄ and T₃ hormones levels decrease with age between the groups. There was a significant correlation between T₄ and T₃ ($r=+0.347$, $P= 0.0001$).

The association of TSH with T₄ and T₃ concentration was also studied, there was an inverse association ($r= - 0.331$, $P=0.0001$, $r= - 0.345$, $P= 0.0001$ respectively).

The positive association between SBP and age is also correlated, higher age is corresponding with increase level of SBP ($r=+0.225$, $P= 0.0001$). DBP was positively associated with age ($r=+0.200$, $P= 0.0001$) and the highest value was in the age range 41-50 years.

Clinic SBP and DBP were significantly higher in patients with hypothyroidism. SBP correlated positively with DBP ($r=+0.657$, $P= 0.0001$). SBP and DBP correlated significantly with T₄ hypothyroid patients ($r=+0.168$, $P= 0.044$; $r=+ 0.177$, $P= 0.036$ respectively).

The positive association between thyroid hormones, blood pressure and age indicate that increasing of TSH level and blood pressure are corresponding to higher age.

We studied the TSH levels of hypothyroidism patients with and without HTA related with age.

Table IV. TSH levels of hypothyroidism patients with and without HTA relation to age

Age	Hypothyroidism	Hypothyroidism - HTA
	TSH(μ UI/ml)	TSH(μ UI/ml)
< 40	3.76 \pm 2.10	3.71 \pm 2.05
41 - 50	5.22 \pm 3.52	5.65 \pm 4.54
51 - 60	5.40 \pm 3.86	11.66 \pm 5.65
>60	6.12 \pm 4.32	12.06 \pm 9.23

Hypothyroidism was defined on the basis of elevated serum TSH levels and minor degree in the absence of obvious clinical features of hypothyroidism. TSH levels vary with age increased markedly after the age of 40 years.

Serum TSH hormone was higher in subjects with hypothyroid- HTA than hypothyroid without HTA. Positive association between TSH hypothyroidism- HTA and age we found ($r: +0.353$, $P= 0.0001$).

Discussion

Variability of thyroid hormone level modifies molecular pathways in the heart and vasculature causes relevant cardiovascular diseases. Cardiovascular system responds to the minimal changes in circulating thyroid hormone levels, which are typical of individuals with clinical thyroid dysfunction [1, 4-6]. Previous epidemiological studies examining the association between hypothyroid dysfunction and cardiovascular diseases [13, 16].

Hypothyroidism is frequently accompanied by increased vascular resistance, and a greater prevalence of hypertension. Treatment of hypothyroidism may lead to normalization of blood pressure, although some patients may exhibit sustained hypertension. The mechanism of this condition could be the alterations produced in aortic stiffness. The prevalence of systemic hypertension is nearly three-fold higher in patients with hypothyroidism. In addition, in patients with systemic hypertension, overt hypothyroidism is associated with higher blood pressure [17-19].

It has been reported that hypertension accompanies hypothyroidism; its prevalence remains to be established since wide-ranging rates from 0 to 50%. In the population studied from our community setting hypothyroidism (35.8 %) occurs in higher percentage of women (81.5%) than of men (18.5%). The probability of developing hypothyroidism increases with age reaching a maximum between the ages of 40 and 50 years.

In the present study we will address the hypothyroid disease from a cardiovascular perspective and the thyroid function tests that are most appropriate to confirm the suspected diagnosis. In addition, we will discuss the data that demonstrate the changes in thyroid hormone metabolism that latter could have implications for the management of patients with arterial blood pressure. SBP and DBP in hypothyroid patients was higher than corresponding age groups were increasing.

The cardiovascular system is sensitive to the action of thyroid hormone. However, a wide spectrum of cardiac abnormalities has long been recognized in patients with overt thyroid dysfunction, the question of cardiac involvement in patients with thyroid dysfunction has been investigated only in the last two to three decades. In our population, the prevalence of hypothyroidism is significantly higher than other thyroids diseases [20].

We compared the age-related increase of blood pressure in hypothyroid patients. In the present study, the female subjects were most affected indicating that sex-related factors that could influence blood

pressure. In the present study, there were differences in weight, age between sexes in hypothyroid hypertensive patients.

When the hypertension is defined as a blood pressure above 140/90 mm Hg, the prevalence of hypertension was significantly higher in hypothyroid patients. SBP and DBP of hypothyroid patients were significantly higher and age-related. The finding suggests that the hypothyroid state accelerates the age-related increases in blood pressure. In addition, we found an increase in SBP and DBP with increasing concentration of TSH. Then, we found a significantly associated systolic arterial blood pressure with TSH levels in the hypothyroid-hypertensive patients.

The mean of TSH concentration in hypothyroid-hypertensive women was higher than men, above of reference range. Similarly, current reports estimate that it affects of the adult female population and a smaller percentage of adult males. The prevalence of elevated TSH levels in this population was 20.8% and the prevalence of subclinical hypothyroidism was 5.6%. High prevalence of hypothyroidism in our hypertensive patients was detected. We reported in the present study a series of patients had concomitant hypertension and hypothyroidism. Hypothyroidism was defined on the basis of elevated serum TSH levels and minor degree in the absence of obvious clinical features of hypothyroidism. TSH levels vary with age increased markedly after the age of 40 years. We described a high retrospective prevalence of hypothyroidism or elevated levels of TSH in patients with hypertension. The study provides a pathogenic relationship between hypertension and thyroid disease.

Decrease of serum T_4 and T_3 suggest the lack of blood pressure regulation which could be responsible for the hypertensive state. In the present study, thyroid hormones were considered since their average T_4 and T_3 levels were decreasing with age. Thyroid hormone deficiency should merit some consideration in the initial evaluation of the hypertensive patients.

The mean SBP and DBP variability was also significantly higher in patients with hypothyroidism. Furthermore, significant correlations between systolic and diastolic blood pressure and either T_4 or T_3 , suggest that thyroid hormone deficiency could contribute to increase in blood pressure.

The positive association between thyroid hormones, blood pressure and age indicate that increasing of TSH level and blood pressure are corresponding to higher age. These results suggest a close association between hypertension and hypothyroidism.

The mechanism of increased blood pressure in hypothyroidism is not known; however, structural

changes of vascular tissue by thyroid hormone deficiency could be a local factor in causing a higher peripheral resistance. Furthermore, alterations in autonomic nervous function by changes in the thyroid hormones levels that could contribute to the development of hypertension by enhancing norepinephrine release. However, other multiple local factors could be involved in this mechanism.

Patients with HTA should be investigated for the possibility of coexisting hypothyroidism. These results confirm that thyroid dysfunction is common, may often go undetected, and may be associated with adverse health outcomes that can be avoided by serum TSH measurement.

In conclusion, we found a positive association between TSH and SBP that could have implications for cardiovascular health. These findings indicate that hypothyroidism may be an important predictor of higher mean SBP. In these population patients we found that hypertension could be associated with the presence of hypothyroidism.

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