HYPERTENSION IN HYPOTHYROIDISM, A RESPONSE TO REPLACEMENT THERAPY WITH L-THYROXINE

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ABSTRACT

Objective: **To study the association between hypertension and hypothyroidism.**

Patients and Methods: **Sixty two female patients enrolled in this study were selected from eighty three patients consulted the Endocrine and Diabetic Center in Al-Mawani General Hospital during the period from January 2009 to December 2011 and presented with features of hypothyroidism. Each patient was interviewed, examined for body mass index and blood pressure measurements. Twenty one patients were excluded from the study fasting blood samples were analyzed to determine FT3, FT4, TSH, prolactin and total cholesterol levels.**

Results: **The level of systolic and diastolic blood pressure in overt hypothyroidism in comparison to subclinical hypothyroidism showed a dramatic response to thyroxine replacement. Mean difference (95% CI after treatment with L-thyroxine for systolic (SBP) (19.78-29.31 mmHg) and (10.98-17.07 mmHg) for diastolic blood pressure (DBP) in overt hypothyroidism, while the mean difference (95% CI in subclinical form is (2.79-8.49 mmHg) for systolic (SBP) and (0.1-3.24 mmHg) for diastolic (DBP) blood pressure.**

Conclusion: **Systolic and diastolic hypertension in hypothyroidism is a common association but the response of blood pressure to replacement with thyroxine was significant in overt hypothyroidism in comparison to subclinical hypothyroidism, while only systolic component had responded to replacement therapy in subclinical type.**

INTRODUCTION

Hypothyroidism has long being considered as one of the secondary causes of hypertension.[1] The role of thyroid hormone in heart and vascular physiology has been investigated since the description of first cardiovascular symptoms associated with dysthyroid patients. Arterial hypertension is associated with both hypo- and hyperthyroidism,[2] suggesting different working mechanisms in the two conditions. The most common type of hypothyroidism is that caused by primary thyroid gland failure. One of common clinical signs observed in hypothyroid and hyperthyroid patients is the changes in their blood pressure.[3] Many factors may contribute to these associations.[4,5] Arterial stiffness is an important determinant of arteriosclerosis and changes in arterial wall elasticity, and may occur before or during the early stages of atherosclerosis. Increased arterial stiffness of the central artery leads to an increase in systolic blood pressure but not diastolic part of the cycle of hypertension and this might explain the association between hyperthyroidism and wide pulse pressure but not for hypothyroidism. On the other hand, the increased systolic and diastolic BP could induce changes in the arterial wall, reducing elasticity and increasing stiffness. Adequate thyroid hormone replacement therapy successfully reduced BP, supporting the secondary cause of hypertension in patients with hypothyroidism.[6,7] 3,5,3'-triiodothyronine (T3) represents the metabolically active thyroid agent that possibly has a vasodilatory effect on the vascular muscle cells.[8] T3 deficiency is associated with peripheral vasoconstriction.[9] Thyroid hormones potentiate β-adrenergic response by increasing the number of β-adrenoreceptors with an opposite action on α-adrenergic receptors.[10] In the hypothyroid state, the density of α_1-adrenoreceptors is increased while β-adrenoreceptors are reduced in vascular beds. Actions of α_1-adrenoreceptors mainly involve smooth muscle cell contraction, causing vasoconstriction in the blood vessels. Plasma vasopressin is found to be elevated in hypothyroid patients, that may explain the water retention that occurs in hypothyroid subjects.[11] Thyroid dysfunctions can interact with other systems involved in cardiovascular regulations.

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In fact beside sympathetic activities, thyroid hormones can increase angiotensinogen,[12] a trial nitreurtric peptide level[13,14] and vasopressin levels.[15,16] More complex is the effects of thyroid hormone on renal function. Hypothyroidism leads to reduction in glomerular filtration rate and to a decrease in renal blood flow.[17,18] High serum prolactin and TSH concentrations, seen in patients with hypothyroidism, suggest a reduced dopaminergic activity in the central nervous system that could contribute to the development of hypertension by enhancing nor-epinephrine release. Normalization of central dopaminergic activity by thyroid hormone replacement therapy could be one factor responsible for reduction in blood pressure in the hypertensive hypothyroid patients.[19,20]

The study was aiming to find the association between hypertension and hypothyroidism and the effect of treatment with thyroxine on blood pressure.

PATIENTS AND METHODS

This is a prospective cross sectional facility based study carried on sixty two elected patients of female gender, their ages range from 15 to 58 years, with a mean 39.65years.They consulted Al-Mawani General Hospital, Endocrine and Diabetic Center in Basrah, Southern Iraq during the period from January 2009 to December 2011.The study was approved by Department of Medicine, Basrah College of Medicine. Male patients, and patients with diabetes, ischemic heart disease, renal disease, smoker, pregnant women and morbidly obese were excluded. Only sixty two patients were eligible for the study. Each patient was subjected to full history and clinical examination including single observer arterial blood pressure measurement in seated position in both hands after five minute rest and elbow was slightly flexed and the highest result is considered abnormal using mercury type sphygmomanometer. Blood pressure of 140mm Hg or was considered abnormal for systolic (SBP) and equal or more than 90 mm Hg was considered abnormal for diastolic (DBP). Anthropometric measures were made with the patients wearing light weight clothes with no shoes height. Body mass index (BMI) was calculated as weight in kilogram over squared height in meters. Serum concentration of TSH, free T4 and free T3 were measured using an automated immunoassay analyzer (miniVIDAS). Total cholesterol, plasma glucose and prolactin were measured using standard techniques. All patients measurements were done in fasting state at baseline and after 6 months of thyroxine replacement therapy. Patients were classified in two groups;

Group A: Those with high level of TSH and significantly low FT3 and FT4.

Group B: Those patients with slightly elevated TSH and normal FT3 and FT4.

All patients in both groups received full dose of thyroxine in gradually building doses with informed consents. Patients were followed at monthly intervals and interviewed for symptoms. Recording of blood pressure and TSH estimations were made for six months and the final blood pressure record was considered the end result of the study. Data were fed on a computer and analyzed using the Statistical Package for Social Sciences (SPSS version 15). The mean±SD was computed for comparing the results. The distribution of cases among various criteria was presented by their percentage. The comparison of means between two groups was tested by paired t-test. Results were considered statistically significant if P-value is less than or equal to 0.05.

RESULTS

Patients physical characteristics and anthropometric measures were presented in (Table-1). No difference between the two groups was found as they were carefully matched in physical criteria. Participants in this study belong to female gender as the disease is more common in female patients on one hand and male patients are excluded from study to

exclude sex effects on blood pressure on the other hand.

Table 1.General characteristics of the study subject.

Variable	Group 'A' (n=31)	Group 'B' (n=31)	P-value
Age (Years)	39.00±9.07	40.61±9.13	0.523
Sex (female)	31(100%)	31(100%)	-
Body mass index (kg/m^2)	30.96±6.83	33.58±4.73	0.106

Body mass index and age were matched for the same reasons. Overt hypothyroidism group showed markedly elevated TSH and suppressed FT3 and FT4 levels in comparison to marginally elevated TSH and normal levels of FT3 and FT4 in subclinical group (Table-2).

Table 2. Comparison of laboratory results between overt and subclinical hypothyroid groups.

Variable	Group 'A' (n=31)	Group 'B'(n=31)	P-value
TSH (m.IU /L)	44.15±24.90	6.19±1.22	0.000
FT4 (IU /ml)	2.07±0.81	4.79±0.50	0.000
FT3 (IU /ml)	0.50±0.24	1.67±0.35	0.000
T. cholesterol(mg /dl)	211±26.77	207±48.80	0.629
S.Prolactin (ng/ ml)	18.37±8.05	11.47± 6.47	0.001

Total cholesterol levels were marginally increased in both groups, though statistically was not significant. The study demonstrated an increased mean prolactin levels in overt group (A) in comparison with subclinical group (B); the difference was statistically significant. Both groups: overt group (A) and subclinical hypothyroidism group (B) showed an increase in systolic and diastolic blood pressure when first interviewed (Table-3) though overt hypothyroidism demonstrated diastolic and systolic predominance over subclinical group but it did not reach statistical significance. However, the study demonstrated dramatic response of blood pressure in group A to replacement with thyroxine in both systolic and diastolic components (p-value <0.05). In comparison to the response of systolic component only in group B. However this difference was not statistically significant. Diastolic blood pressure in group B patients did not demonstrate any response to replacement with thyroxine.

Table 3.Comparison of mean systolic and diastolic blood pressure between overt and subclinical groups before and after thyroxine therapy.

Variable	Group 'A' (n=31)	Group 'B'(n=31)	P-value
Diastolic B.P before (mmHg)	94.67±6.31	93.54±7.54	0.551
Diastolic B P after (mmHg)	80.64±7.49	92.16±5.34	0.000
Systolic B.P before (mmHg)	151.61± 13.80	143.41±13.87	0.053
Systolic B.P after (mmHg)	127.41±17.91	140.74±12.31	0.003

DISCUSSION

The main purpose of this study is to investigate the relationship between hypothyroid status and the blood pressure changes in the absence of known previous cardiovascular, renal disease and morbid obesity. Most of patients showed high reading blood pressure in both systolic and diastolic components and the increased in either systolic or diastolic component in minority of patients. This gives a strong evidence in that the clinical state of hypothyroidism is strongly associated with hypertension. Additionally, only patients without previous systemic diseases to reduce the effect on blood pressure as it is adversely affected by many systemic conditions or their therapy. The main finding in this study is that thyroid hormone replacement in highly deprived patients in overt hypothyroidism resulted in a dramatic response of both systolic and diastolic blood pressure which paralleled the clinical improvement. This gives a clue to the importance of thyroid hormones in reducing blood pressure, which is regarded as one of important secondary causes of hypertension. The mechanisms underlying this response are not fully understood, but increase in systemic vascular resistance (SVR) and arterial stiffness may accompany low thyroid function.[4,5,8] It has been shown that the thyroid hormone have direct vasodilator effect on vascular muscle cell.[7] On the other hand the response of only the systolic component of blood pressure which was statistically not significant and the absence of response in diastolic component in subclinical hypothyroidism, might support the fact that in this type, the patients are not actually deprived from thyroid hormones and the replacement, though full, does not produce dramatic result in decreasing the blood pressure. It might also support the possibility of other factors that may play a role such as hypercholesrolemia and hyperprolactinemia. [19,20] In the Colorado study, total cholesterol levels were higher in subjects with subclinical hypothyroidism.[21] However no difference in total cholesterol in our subjects was found among groups suggesting qualitative changes that may include small density lipoprotein which is recognized to be proatherogenic. Thyroxine may modify cardiovascular risk and blood pressure through changes in lipid architectures.[22] This may explain the partial improvement in the subclinical type. This study in comparison with other studies showed close association between the replacement with L.thyroxine and blood pressure response in overt hypothyroidism, However, others have failed to demonstrate any association between blood pressure and subclinical hypothyroidism.[23] The rapid response of blood pressure in overt hypothyroid patient to thyroxine in comparison to subclinical may be attributed to their higher prolactin levels, which was reduced after thyroxine replacement therapy.

In conclusions: A parallel reduction of both systolic and diastolic blood pressure in overt hypothyroid patients was found after starting thyroxine therapy in recommended doses. This did not occur in patients with subclinical hypothyroidism. A large controlled trial may be needed to study whether the first group will continue in improvement or not.

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REFERENCES

1. **Klein I. Thyroid hormone and high blood pressure. In: Endocrine Mechanisms in Hypertension Laragh JH, Brenner BM, Kaplan NM (Eds). Raven Press, NY, USA (1989).**
2. **Endo T, Komiya I, Tsukui T, Yamada T, Izumiyama T, Nagata H, R-reevaluation of a possible high incidence of hypertension in hypothyroid patients. Am Heart J. 1979; 98: 684–688.**
3. **Dagre AG, Lekakis JP, Papaioannou TG *et al.* Arterial stiffness is increased in subjects with hypothyroidism. Int. J. Cardiol.2005; 103: 1–6.**

4. Luboshitzky R, Aviv A, Herer P, Lavie L Risk factors for cardiovascular disease in women with subclinical hypothyroidism. Thyroid. 2002; 12: 421–425.
5. Owen PJ, Sabit R, Lazarus JH. Thyroid disease and vascular function. Thyroid.2007; 17: 519–524.
6. Ichiki T. Thyroid hormone and atherosclerosis. Vascul. Pharmacol.2010; 52:151–156.
7. Park KW, Dai HB, Ojamaa K, Lowenstein E, Klein I, Sellke FW. The direct vasomotor effect of thyroid hormones on rat skeletal muscle resistance arteries. Anesth. Analg.1997; 85(4): 734–738.
8. Obuobie K, Smith J, Evans M *et al.* Increased central arterial stiffness in hypothyroidism.J.Clin. Endocrinol. Metab. 2002; 87(10): 4662–4666.
9. Larsen PR, Berry MJ. Nutritional and hormonal regulation of thyroid hormone deiodinases. Annu. Rev. Nutr. 1995: 323–352.
10. Gunasekera RD, Kuriyama H. The influence of thyroid states upon responses of the rat aorta to catecholamine's. Br. J. Pharmacol. 1990; 99: 541–547.
11. Skowsky WR, Kikuchi TA. The role of vasopressin in the impaired water excretion of myxedema. Am. J. Med.1978; 64: 613–621.
12. Levey GS Catecholamine sensitivity, thyroid hormone and the heart: a reevaluation. Am J Med.1971; 50: 413–420.
13. Polikar R, Burger AG, Sherner U, Nicod P. The thyroid and the heart: a reevaluation. Circulation. 1993; 87:1435–1441.
14. Dzau VJ, Herrmann HC Hormonal control of angiotensinogen production. Life Sci.1982; 30:577–584.
15. Zamir N, Slover M, Ohman KP. Thyroid hormone restores atrial stretch induced secretion of atrial natriuretic peptide in hypophysectomized rats. HormMe tab Res.1993; 25:152–155.
16. Sergev O, Racz K, Varga I, Kiss R, Futo L, Mohari K, Glaz E.Thyrotropin releasing hormone increases plasma a trial natriuretic peptide levels in humans. J Endocrinol Invest. 1990; 13: 649–652.
17. Skowsky RW, Kikuchi TA. The role of vasopressin in the impaired water excretion of myxedema. Am J Med.1978; 64:613-621.
18. Hanna FWF, Scanlon MF. Hyponatraemia, hypothyroidism and the role of arginine-vasopressin. Lancet. 1997; 350: 755–756.
19. Kolloch R. Kobayashi K, DeQuattro V Dopaminergic control of sympathetic tone and blood pressure Evidence in primary hypertension. Hypertension. 1980; 2:390.
20. Omae T. Ueda K. Nakashima T, lnoue K: Latent hypothyroidism as a possible cause of hypertension? Abstract of eighth scientific meeting of the International Society of Hypertension. Milan. 1981: 166.
21. Canaris G, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch. Int. Med.* (2000); 160(4): 526–534.
22. Ladenson PW, Cohen HD, Singer PA, Ain KB, Bagchi N, Bigos ST, etc. Screening for thyroid dysfunction in the elderly. Arch Intern Med. 2001; 161:130.
23. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, etc. Subclinical thyroid dysfunction and blood pressure: a community-based study. ClinEndocrinol. 2006; (Oxf) 65: 486–491.