Journal University of Kerbala , Vol. 15 No.3 Scientific . 2017

Role of autoimmunity in directing clinical cardiovascular & serum lipid changes in primary hypothyroidism

دور المناعة الذاتية في تغيرات السريرية القلبية الوعائية وتغير مصل الدهون في ضمور الغدة الدرقية الابتدائي

Dr. Ammar Jabbar Hamad Al-Shammary, MBChB, DM, FIBMS
Kufa University/ College of Medicine

Abstract:

A Study was done to investigate the clinical cardiovascular & serum lipid changes in thyroid peroxidase antibodies (TPO)-positive with primary hypothyroidism on thyroxine treatment. Fifty four patients (31 females & 23 males) with primary hypothyroidism & on thyroxine treatment with were recruited, their ages ranged 45-65 years**.** They were divided into 2 groups according to the result of TPO determination, i.e, TPO-positive & TPO negative groups. Results showed that heart rate was significantly decreased while the blood pressure (both systolic & diastolic) was significantly increased in TPO-positive group in supine & standing position. Serum total cholesterol, low density lipoprotein and high density lipoprotein was significantly reduced in TPO-positive group while serum triglyceride levels were higher in TPO-positive group when compared with those of the TPO-negative group. In conclusion, cardiovascular abnormalities were evident to be more in TPO-positive patients as compared to the TPO-negative hypothyroid patients. Thus, autoimmunity is implicated in cardiovascular and serum lipid changes in hypothyroidism.

الخلاصة:

الدراسة للتغيرات السريرية في القلب والأوعية الدموية (معدل النبض وضغط الدم وانخفاض ضغط الدم الوضعي) وقياس نسبة الدهون في الدم لدى المرضى ذوي النتائج الإيجابية والسلبية TPO .أربعة وخمسين مريضا (31 إناث و 23 ذكور) اعمارهم تتراوح بين 45-65 سنة في هذه الدراسة ، وكان كل منهم لديه قصور الغدة الدرقية الابتدائي ويتعالج ب هرمون الغدة الدرقية ل(6- 30 شهرا)،تم تقييمهم من حيث التاريخ الطبي المفصل والفحص السريري وتقسيمهم وفقا لنتائج TPO إلى مجموعتين؛ TPO إيجابية وTPO مجموعة السلبية و تم الحصول على النتائج التالية **:** معدل ضربات القلب تختلف اختلافا معنويا بين المجموعتين ، وهي أقل في مجموعة TPO الإيجابية. ضغط الدم (الانقباضي و الانبساطي) هي أعلى في المجموعة الإيجابية . مصل الكوليسترول الكلي (TC)، البروتين الدهني منخفض الكثافة (LDL)، البروتين الدهني عالي الكثافة (HDL) فيه انخفاض معنوي في المجموعة الإيجابية بالمقارنة مع المجموعة السلبية. كانت الدهون الثلاثية في الدم (TG) عالية في كل من المجموعتين مع اختلاف كبير للغاية وأعلى في المجموعة إيجابية .نستنتج من ذلك ان مشاكل القلب والأوعية الدموية أكثر في مجموعة TPO الإيجابية بالمقارنة مع المجموعة السلبية.

Introduction :

Primary hypothyroidism is thyroid hormone deficiency caused by defect in the thyroid gland which is common endocrine disease. The prevalence of hypothyroidism is 3.8%–4.6% [1]. The most common cause of primary hypothyroidism is autoimmune thyroiditis (Hashimato′s thyroiditis) in Western countries but iodine deficiency remains an important cause in some areas,other causes of hypothyroidism include thyroidectomy, radioiodine therapy, and drugs such as amiodarone and others **[2].** Clinical features of hypothyroidism include tiredness, malaise, weight gain, cold intolerance, constipation, proxymal muscle weakness, dry skin, hoarse voice, poor memory, bradycardia & diastolic hypertension **[3].** Primary hypothyroidism confirmed biochemically by serum thyroid stimulating hormone (TSH) concentration above normal with low free T4 while TSH is high with normal T4 this indicate subclinical hypothyroidism **[4].** Treatment of hypothyroidism by oral levothyroxine replacement therapy **[5].** The aim for a TSH in the lower half of the normal range, typically <2.5 mIU/L**[6].** Delayed untreated hypothyroidism can cause persistent

bradycardia, high atherogenic lipid and impairment in myocardial function. Oral levothyroxine have positive inotropic and chronotropic effect on the heart so starting a full dose of it may cause acute coronary syndrome in hypothyroid patients with hidden coronary artery disease **[7,8] .** Autoimmune thyroiditis causes >90% of all noniatrogenic causes of hypothyroidism **[9] .** Antibodies against thyroid peroxidase (TPOAbs) are detected in 90% of all patients with Hashimoto′s thyroiditis **[10]** ,which result from autoimmunity against thyroid autoantigens, thyroglobulin (Tg) and thyroid peroxidase (TPO)**[**11**]** .Thyroid hormone has a main effect in the cardiovascular system function and cardiac hemodynamic and to maintain the cardiovascular homeostasis **[**12**].**Cardiovascular morbidities are common in hypothyroidism however the pathophysiologic mechanisms of cardiovascular dysfunctions in this condition has not yet been fully explained . The reported increased cardiovascular defects in hypothyroidism possibly attributable to chronic sympathovagal imbalance, inflammation, obesity, insulin resistance and increased plasma level of insulin, C-peptide and lipoproteins **[13] .**Hypothyroidism seems to evoke a hypoadrenergic state cause bradycardia, decrease basal metabolism ,cardiac output, and the intracellular catecholamine assembly from circulation **[14].** Increase diastolic blood pressure because an increased systemic vascular resistance, but blood pressure kept nearly stable because of decreased cardiac output, diastolic dysfunction in rest as well as systolic dysfunction at stress, hypercholesterinaemia and diastolic hypertension in hypothyroid patients can initiate arteriosclerosis and coronary heart disease (CHD). **[**15] . Subclinical hypothyroidism is linked with an initial reduced systolic function, diastolic hypertension, increased systemic vascular resistance, an atherogenic lipid profile, and inflammatory condition **[**16**].** Such thyroid dysfunctions lead to changes in the lipoprotein metabolism & initiate cardiovascular diseases by increase the total cholesterol and low density lipoprotein cholesterol, LDL-C levels[**17].**

Aim of the study :

Evaluation of clinical cardiovascular changes (pulse rate& blood pressure)& serum lipid changes in TPO- positive & TPO-negative patients with primary hypothyroidism.

Method :

In this study, total 71 patients (30 males & 41 females) with primary hypothyroidism, their age ranging from 40-65 years . The study were done in Diabetes & Endocrine center in Al-Sader teaching hospital in the period between 10th september 2014 to 24 th october 2015 . All patients previously diagnosed to have primary hypothyroidism by thyroid function test (TFT) with duration of disease ranging between 6-30 months. All patients participated in study were on levothyroxine maintenance dose ranging between (50- 200 microgram/once daily , oral tablet) according to their thyroid function test results . All patients evaluated by detailed medical history, physical examination, ECG& biochemical laboratory investigation in form of **f**asting blood sugar , blood urea and serum creatinine .To exclude patients with the following from the study (exclusion criteria):Diabetes Mellitus, renal failure, hypertension, Ischemic heart disease before diagnosis of hypothyroidism, smoker & alcoholic, valvular heart disease .So 17 patients excluded from the study & 54 patients (31 females & 23 males) age ranging between 45-65 years were included in this study, all of them evaluated by the following tests & investigations .Heart rate measure by figure tip pulse oximeter (Utech.ltd .china) & blood pressure measured by sphygmomanometer (rossmax international Ltd /Switzerland) measured for patients in supine & upright position (after 2 min standing) . Fasting blood samples for at least 12 hours were collected, 6 ml of blood was drawn.

1.Thyroid peroxidase(TPO) autoantibodies measurements :

anti-TPO autoantibodies were determined by using ELISA kits AESKULISA a-TPO (AESKU.DIAGNOSTICS, Wendelsheim, Germany) is a solid phase enzyme immunoassay for the quantitative and qualitative detection of antibodies against TPO in human serum . results were considered normal IgG/IgM <40 U/ml, equivocal IgG/IgM 40-60 U/ml, positive IgG/IgM >60 U/ml . according to these results , patients included in the study divided into two groups :TPO positive group consist of 30 patients & TPO negative group consist of 24 patients .

2. Serum lipid measurements:

Blood was drawn after a 12-hour fast , total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured directly and low-density lipoprotein (LDL) cholesterol measured by help of the Friedewald equation. LDL cholesterol = Total cholesterol – HDL cholesterol – Total triglyceride ÷ 2.2

Statistics:

Data analyzed by using SPSS computerized program version (20) in results data articulated as mean +_ standard deviation . independent sample T-test used to compare two groups data analysis & Chi- square used to analyze discrete data . P-value considered statistically significant if < 0.05 .

Results :

1. Demographic variables of patients participated in the study:

The result of this study include 54 patients with primary hypothyroidism on thyroxine treatment , 30 of them were TPO- positive and 24 TPO- negative. The demographic parameters of patients including gender distribution, age, BMI & duration of disease show insignificant differences (p > 0.05) between TPO- positive & TPO- negative groups This demonstrated in table (1) & (2)

Table(1) Gender distribution of studied patients in both TPO positive and negative groups .

		Group		P value
		TPO Positive	TPO Negative	
Gender	Female	17	14	0.91
		56.67%	58.33%	
	Male	13	10	
		43.33%	41.67%	
Total		30	24	
		100.0%	100.0%	

Table(2) Comparison between TPO positive and negative groups in different demographic parameters .

Parameter	TPO positive	TPO negative	P value
	Mean ±SD	Mean ±SD	
Age/years	57.50±7.990	53.75±5.674	0.06
BMI Kg/m2	37.33±10.721	35.32±9.33	0.472
Duration of the disease/years	1.50±0.601	1.375±0.824	0.552

Values expressed as mean ± SE .

2. Heart rate & blood pressure :

In this study there were significant differences (P < 0.05) in heart rate between two groups in both supine & standing position, heart rate lower in TPO- positive group. Blood pressure (both systolic & diastolic) are higher in TPO- positive group in supine & standing position with significant differences (P < 0.05) between two groups in supine blood pressure (systolic & diastolic) . There was highly significant difference (P < 0.001) in diastolic blood pressure (standing position) in TPO- positive group as compared to TPO- negative group &there was non significant difference (P > 0.05) in systolic blood pressure (standing position) in TPO- positive group as compared to TPO- negative group. These result was shown in Table (3) .

Table (3) Comparison between TPO positive and negative in heart rate & blood pressure in both supine & standing position .

Parameter	TPO positive	TPO negative	P value
	Mean ±SD	Mean ±SD	
heart rate supine (beats/min)	68.0±19.684	76.50±4.125	0.025*
heart rate standing(beats/min)	72.00±16.264	83.03±4.421	0.001*
Systolic BP supine(mmHg)	135±8.5	127.8±1.89	0.005*
Systolic BP standing (mmHg)	130.67±12.35	129.2±7.69	0.626
Diastolic BP supine (mmHg)	91.3±4.8	87.4±6.71	0.003*
Diastolic BP standing (mmHg)	90.6±7.8	82.9±4.91	<0.001**

Values expressed as mean ± SE .
* Significant p value **Highly significant p value

3 .Serum lipid results :

Serum Total cholesterol (TC) was significantly reduced ($P < 0.05$) in TPO- positive group as compared to TPO- negative group . Serum high density lipoprotein (HDL) was significantly reduced in TPO- positive group & serum low density lipoprotein (LDL) had highly significant reduction($P < 0.001$) in same group as compared with TPO- negative group . Serum triglyceride (TG) results were high in both groups with highly significant difference . Level of serum triglyceride was higher in TPO- positive group. These result was shown in Table (4) .

Table (4) : Comparison between TPO positive and negative groups in serum lipids .

Parameter	TPO positive	TPO negative	P value
	Mean ±SD	Mean ±SD	
Cholesterol mg/dl	168.86±19.473	185.00±16.847	0.002*
TG mg/dl	219.66±37.863	166.50±17.312	<0.001**
HDL mg/dl	37.40±6.371	41.00±5.149	0.029*
LDL mg/dl	86.00±25.173	110.70±15.094	<0.001**

Values expressed as mean ± SE .
* Significant p value **Highly significant p value

Discussion:

The demographic data of patients participated in this study show matched gender in two groups, also there was no significant changes among two groups in age, BMI & duration of primary hypothyroidism, these are crucial points to eliminate effect of these variables on the results de this study . In this study there were significant differences ($P < 0.05$) in heart rate among two groups in both supine & standing position, heart rate lower in TPO- positive group. Many studies found that untreated hypothyroid patient had bradycardia since autonomic neuropathy in hypothyroidism is due to increased vagal tone although this can be partly subsides with thyroxine therapy **,** all patients included in the study on thyroxine treatment & this explained why they are not have bradycardia , moreover to probable effect of autoimmunity in TPO- positive group on autonomic organize on the pulse [18] .Blood pressure (both systolic & diastolic) are higher in TPO- positive

group in supine & standing position with significant differences ($P < 0.05$) involving two groups. Postural hypotension not found in any patient for both groups .Some researches found that hypothyroidism lead to elevation in blood pressure especially diastolic blood pressure for the reason that it decreases endothelial mediated vasorelaxation and vascular compliance, furthermore hypothyroidism cause rise in blood pressure in consequence of its effect on increasing peripheral vascular resistance[19] .Blood pressure (both systolic & diastolic) are higher in TPO- positive, as well thyroid antibodies in autoimmune thyroditis have been related with increased markers of endothelial dysfunction that may produce atherosclerosis [20].Serum Total cholesterol(TC), low density lipoprotein (LDL) & high density lipoprotein (HDL) was significantly reduced in TPO-positive group as compared to TPO- negative group . Serum triglyceride (TG) results were high in both groups with highly significant difference ($P < 0.001$) & level of triglyceride was higher in TPO- positive group .Studies **a**ffirmed that autoimmune hypothyroidism associated with hyperlipedemia and recommended that hypothyroidism can lead to arteriosclerosis by rising the total cholesterol and low-density lipoprotein because low-density lipoprotein cholesterol receptors found in fibroblasts, the liver and in other tissues that the hypothyroid cannot attract low-density lipoprotein as well as the euthyroid . Thus, this material accumulates in the circulation. With thyroid hormone therapy, unpleasant effects can be prohibited and total cholesterol and low-density lipoprotein values can be reduced .This may explain result of our study as all patients on thyroxine replacement therapy [21] .Studies bring into being the incidence of hyperlipidemia was more in hypothyroidism in the company of antibodies for thyroid peroxidase. furthermore, the low-density lipoprotein level was found to decreased by approximately 12% on thyroid hormone therapy, the total cholesterol also drop , & this found prominently when thyroid auto-antibodies are present .The bigger the severity of hypothyroidism, the bigger the effects of the levothyroxine upon hyperlipidemia if thyroid autoantibodies are positive. This may explain lipid results of our study as all patients on thyroxine replacement therapy and found that autoimmune thyroditis cause elevation in TC, TG, LDL without effect on HDL . But serum lipids significantly reduced after thyroxine replacement . Treatment of hypothyroidism may normalize the lipid profiles[22].

Conclusion :

1. There is correlation between TPO- positive hypothyroid patients and the clinical cardiovascular abnormalities in form of low heart rate and higher systolic , diastolic blood pressure with more postural drop in pressure .
2. Thyroid replacement therapy for TPO- positive hypothyroid patients had more effect on decrease total cholesterols and LDL- cholesterol .

Recommendations :

1. We recommend to evaluate the auto antibodies inform of anti TPO in hypothyroid patient as they more related to cardiovascular clinical complications than those negative for anti TPO .
2. Measurement of lipid profile before and after thyroid replacement therapy to evaluate the effect of autoimmunity on the response and role of statin therapy .
3. Future studies for fallow up anti TPO positive hypothyroid patients for coronary artery disease and possible role of immune modulating agents as compare to anti TPO negative patient .

References :

1. Leese GP, Flynn RV, Jung RT,et al. Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: the Thyroid Epidemiology Audit and Research Study (TEARS) . Clin Endocrinol. 2008;68(2):311–316.
2. Roberts CG, Ladenson PW. Hypothyroidism. Lancet. 2004;363(9411):793–803.
3. Canaris GJ, Manowitz NR, Mayor G, et al . The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160(4):526–534.
4. Spencer CA, Hollowell JG, Kazarosyan M, et al . National Health and Nutrition Examination Survey III thyroid-stimulating hormone (TSH)-thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction. J Clin Endocrinol Metab. 2007;92(11):4236–4240.
5. Bolk N, Visser TJ, Kalsbeek A,et al . Effects of evening vs morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients. Clin Endocrinol. 2007;66(1):43–48 .
6. Vaidya B, Pearce SH. Management of hypothyroidism in adults. BMJ. 2008;337:a801.
7. Danzi S, Klein I. Thyroid disease and the cardiovascular system. Endocrinol Metab Clin North Am. 2014;43(2):517–28.
8. McGrogan A, Seaman HE, Wright JW, et al . The incidence of autoimmune thyroid disease: a systematic review of the literature. Clin Endocrinol 2008;69:687–696 .
9. Anthony P Weetman, Adv Anat Pathol. The Immunopathogenesis of Chronic Autoimmune Thyroiditis One Century after Hashimoto . Eur Thyroid J. 2013 Jan; 1(4): 243–250.
10. Sandeep Chopra, Davis Cherian, and Jubbin J. Jacob . The thyroid hormone, parathyroid hormone and vitamin D associated hypertension . Indian J Endocrinol Metab. 2011 Oct; 15(Suppl4): S354–S360 .
11. Holly Aliesky, Cynthia L. Courtney, Basil Rapoport .Thyroid Autoantibodies Are Rare in Nonhuman Great Apes and Hypothyroidism Cannot Be Attributed to Thyroid Autoimmunity . Endocrinology. 2013 Dec; 154(12): 4896–4907.
12. Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007;116(15):1725–35.
13. Avupati Naga Syamsunder, Gopal Krushna Pal, Pravati Pal,et al . Association of Sympathovagal Imbalance with Cardiovascular Risks in Overt Hypothyroidism . Am J Med Sci. 2013 Sep; 5(9): 554–561.
14. Grais IM, Sowers JR. Thyroid and the heart. Am J Med. 2014;127(8):691–8.
15. Wien Med Wochenschr. Thyroid and cardiovascular system. 2005 Oct;155(19-20):436-43 .
16. Ladenson PW. Cardiovascular consequences of subclinical thyroid dysfunction: more smoke but no fire. Ann Intern Med. 2008;148(11):880–1.
17. Fardella C, Poggi H, Gloger S, et al. High prevalence of subclinical thyroidal disease among indivisuals attended in health control. Rev Med Chil. 2001;129:155–160.
18. Grais IM. Bedside skills: A 50-year personal retrospective. Texas Heart Institute J. 2010;37(6):629–632
19. Ira Martin Grais and James R. Sowers. Thyroid and the Heart . Am J Med. 2014 Aug; 127(8): 691–698.
20. Ciccone MM, De Pergola G, Porcelli MT, et al. Increased carotid IMT in overweight and obese women affected by Hashimoto's thyroiditis: an adiposity and autoimmune linkage? BMC Cardiovasc Disord. 2010;10:22.
21. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 2006;295:1033–1041.
22. Zuzana Minarikova, Ludovit Gaspar, Peter Kruzliak,et al . The effects of treatment on lipoprotein subfractions evaluated by polyacrylamide gel electrophoresis in patients with autoimmune hypothyroidism and hyperthyroidism. Lipids Health Dis. 2014; 13: 158.