Original Article

Evaluation of endothelial function in exogenous subclinical hyperthyroidism and the effect of treatment

Sayed Mohammad Hosseini, Elham Khosravi Bakhtyari[1], Kiyan Heshmat-Ghahdarijani[1], Noushin Khalili

Department of Internal Medicine, Isfahan Endocrine and Metabolism Research Center, [1]Department of Cardiology, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Subclinical hyperthyroidism (SHy) is a widespread condition in which cardiovascular manifestations are frequently occur, but there is still a debate about the vascular responsiveness in it. Measuring flow-mediated dilation (FMD) and intimae-media thickness (IMT) are used to evaluate endothelial function in these patients.

Materials and Methods: Twenty-five patients with a diagnosis of exogenous SHy and 25 full matched healthy subjects were enrolled. At first FMD of brachial artery and IMT of common carotid artery were obtained from all the participants. In the second phase, in the second phase of study, the dosage of levothyroxine was reduced at least 25% of prior dosage, and this was continued until thyroid stimulating hormone became normal range. Measuring FMD and IMT was repeated after this intervention in the case group.

Results: The mean age of case and control groups were 38.48 ± 12.05 and 36.72 ± 11.15 years, respectively. The mean of FMD in healthy people was dramatically higher than the subclinical hyperthyroid patients ($P < 0.001$) but no statistically significant difference was found for IMT ($P = 0.459$). After intervention in the case group, FMD was meaningfully increased ($P < 0.001$) but IMT of common carotid artery was not considerably changed ($P = 0.491$).

Conclusions: This study demonstrated that FMD decreased in exogenous subclinical hyperthyroid patients which could be partially restored by treatment. These findings suggest that treatment of subclinical hyperthyroid state could improve endothelial dysfunction and at the end decreased the cardiovascular complications.

Key Words: Endothelial dysfunction, flow-mediated dilation, intima-media thickness, subclinical hyperthyroidism

Address for correspondence:
Dr. Noushin Khalili, Isfahan University of Medical Sciences, Hezarjerib Avenue, Isfahan, Iran. E-mail: n_khalili@med.mui.ac.ir

Received: 09.06.2014, **Accepted:** 20.02.2016

INTRODUCTION

Subclinical hyperthyroidism (SHy) is a widespread condition which is defined as suppressed thyroid stimulating hormone (TSH) concentration while triiodothyronine (T_3) and free thyroxin (FT_4) concentrations are within normal limits.[1] Etiology of SHy is divided into endogenous and exogenous causes that exogenous sources include 58% of all causes.[2,3] Although all symptoms of hyperthyroidism could be

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.194800

How to cite this article: Hosseini SM, Bakhtyari EK, Heshmat-Ghahdarijani K, Khalili N. Evaluation of endothelial function in exogenous subclinical hyperthyroidism and the effect of treatment. Adv Biomed Res 2016;5:173.

seen in SHy with less severity, but most of the patients do not show obvious clinical manifestations.[4] For this frequently occurring condition, exact therapeutic approaches have not yet been established.

Cardiovascular manifestations are well-known components of hyperthyroidism. Hyperthyroidism is associated with increased cardiac output and heart rate, systolic hypertension, reduction in peripheral vascular resistance,[5,6] and impaired vascular elasticity of large and small arteries,[7] but there is still a debate about the vascular responsiveness in SHy.

Recent studies indicate that hyperthyroidism is associated with endothelial dysfunction[8] but the effect of SHy needs to be determined.

Thyroid hormone targeting vascular endothelium may increase blood flow with resultant shear stress of the vessel and changes in endothelial function. T_3 decreases systemic vascular resistance (SVR) by dilating the resistance arterioles of the peripheral circulation. Mechanisms are modulation of nitric oxide (NO) production,[9] and increase of sodium and potassium flux in smooth muscle cells that lead to a decrease in vascular tone.[10] A decrease in SVR then leads to a decrease in the effective arterial filling volume, causing an increase in renin release.[11] This leads to stimulation of renal sodium reabsorption, and plasma volume is increased. Erythropoietin is stimulated by T_3. Because of these effects, blood volume, ventricular preload, and cardiac output increase.[5,12]

Flow-mediated endothelium-dependent vasodilation (flow-mediated dilation [FMD]) of the brachial artery is a functional test of the capacity of increased blood flow, following induced ischemia and, therefore, is a marker of endothelial function.[6] Reactive hyperemia induced by transient ischemia of the forearm may increase blood flow and shear stress of the vessel wall, resulting in the release of endothelial NO, and possibly other vasodilator mediators, and vascular dilation.[13] Measuring intimae-media thickness (IMT) of the carotid artery by ultrasound is another established method for detection of early atherosclerotic changes which has been proven to be directly related to coronary artery disease.[14]

The aim of this study is to compare the endothelial function and carotid artery IMT of SHy patients to euthyroid subjects and whether changes induced by hyperthyroidism can be restored to normal during the euthyroid state following treatment.

MATERIALS AND METHODS

Study populations

Twenty-five patients with diagnosis of exogenous SHy and 25 age and gender-matched healthy subjects[15] according to medical history, physical examination, and routine laboratory tests were enrolled in this study. SHy was defined as normal free and total T_3 and T_4 with suppressed TSH (TSH < 0.3 mIU/L). Euthyroidism was defined as a serum thyrotropin (TSH) level between 0.3 and 4 mIU/L. The normal range of T_3 and T_4 was 76.3–220.8 ng/dl and 4.5–12.6 μg/dl, respectively.

All patients were treated with levothyroxine because of previous hypothyroidism.

Patient who had hypertension, diabetes mellitus, coronary artery disease, infectious disease, known case of liver and kidney diseases, hyperlipidemia, menstrual disorder, polycystic ovary syndrome, morbid obesity (body mass index >30), current smoker of cigarette, alcohol abuser or drug abuser, anemia, and migraine were not included in this study, and this rule was performed for all patients and control subjects.

Exclusion criteria were using any drugs except levothyroxine, pregnancy, and lactation. Furthermore, all participants had not used hormonal contraceptives or vasoactive drugs since 3 months before beginning of this study.

The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol, and all patients gave informed consent before study inclusion.

Study design

In this study, at first FMD and carotid IMT were obtained from all the participants. A high-resolution B-mode ultrasonographic system (ATL ultrasound, HDI 5000, and BOTHELL, Washington, USA) with a linear transducer mid-frequency of 7.5 mHz was used to determine FMD of the brachial artery. An experienced ultrasonographer blinded to case and control groups performed all FMDs. At first; patients lay at rest for 10 min. Then, the baseline brachial artery diameter was determined by locating probe on 4–5 cm above the antecubital fossa of the nondominant arm. After that, a pneumatic tourniquet of a sphygmomanometer was inflated on the most proximal portion of the forearm to a pressure of 300 mmHg for 5 min. The cuff of sphygmomanometer was released and second time of scan was taken during 90 s after deflation of cuff. Diameters of artery were determined at the end of diastolic period with ultrasonic calipers from the edge

of the anterior wall to the edge of the posterior wall of the brachial artery.[16] Two other observers supervised the procedures. Changes in diameter were computed as percentage relative to the baseline diameter. FMD was not measured during menstrual phase in female patients. All the FMDs were performed between 10 am and 12 midday. Furthermore, IMT of common carotid artery was calculated with that ultrasonographic system. The bulb dilation served as a landmark to indicate the border between distal common carotid artery and the carotid bulb. Images were obtained from the distal portion of the common carotid artery, 1–2 cm proximal to the carotid bulb. Two bright echogenic lines were defined as intimae and media layers.[14] Three measurements were taken from each subject, and mean value was used for the analysis.

In the second phase, for SHy dosage of levothyroxine decreased 25% of prior dosage and this dose continued for 2 months then TSH was checked. If it was in normal range, rechecked for assurance and if it was not in normal range 25% of last dosage decreased again and go on for next 2 months and this protocol continue until TSH become normal. After this period, all patients were recalled, and complete examination was done, and forearm FMD and carotid IMT was performed with previous ultrasonographic system and the same ultrasonographer. All the laboratory tests were analyzed in Alzahra Biochemistry Laboratory, Isfahan Faculty of Medicine. All the biochemical parameters were analyzed by using immunochemiluminometric assay 2010 SIEMENS ADVIA-century Cp (American).

Statistical analysis

The results are expressed as mean ± standard error. Differences in FMD and IMT between case and control groups were analyzed using the independent-sample *t*-test and differences within the groups (before and after changing levothyroxine dosage) were determined by paired-sample *t*-test. *P* value of 0.05 was considered significant. A statistical software package, SPSS (version 16), was used to perform statistical analysis.

RESULTS

The demographic information

25 exogenous SHy were enrolled in this study as the case group, between October 2012 and July 2013. These patients were treated with levothyroxine for about 78.25 ± 8.89 months. The mean age of these patients was 38.48 ± 12.05 years with a range of 17–60 years and the mean age of control group was 36.72 ± 11.15 years. Both two groups include 20 women and 5 men. No significant difference was observed with respect to age and gender among the study groups. Serum T_4 and T_3 were within normal limits in all subjects, but they were significantly higher in case group ($P < 0.001$). Before reduction of dose of levothyroxine, the control group's mean T_3 and T_4 was 115.32 ± 13.90 ng/dL (minimum: 91; maximum: 150 ng/dL) and 7.73 ± 0.87 μg/dL (minimum: 5.80; maximum: 9.90 μg/dL), respectively. In case group, the mean of T_3 was 142.12 ± 22.96 ng/dL (minimum: 86; maximum: 184 ng/dL) and the mean of T_4 was 9.92 ± 1.22 μg/dL (minimum: 7; maximum: 11.5 μg/dL).

The demographic and metabolic information of these two groups is summarized in Table 1.

Endothelial function markers

The vascular parameters of the both groups (baseline diameter of brachial artery, FMD, and IMT of common carotid artery) are documented in Table 2. As illustrated in Table 2, the mean of FMD in control group (healthy people) was dramatically higher than the subclinical hyperthyroid patients ($P < 0.001$) but no statistically significant difference was found for IMT ($P = 0.459$).

As summarized in Table 3, after intervention in case group and treating SHy, FMD was meaningfully increased ($P < 0.001$) but IMT of common carotid artery was not considerably changed ($P = 0.491$).

Table 1: The general patient's characteristics

Variants	Case	Control	*P*
Age (years)	38.48±12.05	36.72±11.15	0.594
Gender (female/male)	20/5	20/5	<0.001
Height (cm)	163.96±7.07	163.36±5.32	0.736
Weight (kg)	63.04±12.48	58.68±6.5	0.128
BMI (kg/m^2)	23.42±4.24	21.98±2.24	0.141
T_3 (ng/dL)	142.12±22.96	115.32±13.90	<0.001
T_4 (μg/dL)	9.92±1.22	7.73±0.87	<0.001
TSH (mIU/L)	0.15±0.089	2.02±0.41	<0.001
TG (mg/dL)	141.89±11.6	144.52±8.9	0.586
TC (mg/dL)	124.1±15.4	127±19.4	0.784

Data are reported as means±SD or median. BMI: Body mass index, TSH: Thyroid stimulating hormone, TG: Triglyceride, TC: Total cholesterol, SD: Standard deviation

Table 2: Comparison of the flow-mediated dilation parameters and intima-media thickness between case and control groups through the study

Variants	Case	Control	*P*
BBD (mm)	40.96±2.30	33.08±5.67	<0.001
PAD (mm)	42.76±2.38	37.12±6.02	<0.001
FMD (%)	4.41±1.91	12.48±4.46	<0.001
IMT of CCA (mm)	0.61±0.08	0.59±0.08	0.459

Data are reported as means±SD or median. BBD: Basal brachial diameter, PAD: Peak arterial diameter, FMD: Flow-mediated dilation, IMT of CCA: Intima-media thickness of common carotid artery, SD: Standard deviation

Table 3: Comparison of the flow-mediated dilation parameters, intima-media thickness, and thyroid stimulating hormone in case group before and after intervention

Variants	Before intervention	After intervention	*P*
TSH (mIU/L)	0.15±0.08	1.80±0.99	<0.001
BBD (mm)	40.96±2.30	40.76±1.83	0.346
PAD (mm)	42.76±2.38	44.52±2.16	<0.001
FMD (%)	4.41±1.91	9.22±2.13	<0.001
IMT of CCA (mm)	0.61±0.08	0.60±0.08	0.491

Data are reported as means±SD or median. TSH: Thyroid stimulating hormone, BBD: Basal brachial diameter, PAD: Peak arterial diameter, FMD: Flow-mediated dilation, IMT of CCA: Intima-media thickness of common carotid artery, SD: Standard deviation

DISCUSSION

In this study, we wanted to determine whether the endothelial dysfunction measured via FMD can be influenced in exogenous SHy, and if so, what happen when SHy restored to normal during the euthyroid state following treatment. Despite several studies, endothelial dysfunction is not clearly demonstrated in SHy.

In this study, FMD was significantly lower in exogenous SHy compared to demographically matched subjects. The exclusion of participants with concomitant endocrine, renal, hepatic, and other diseases that influence endothelial function allowed us to decrease the effect of confounding variables and yielded a homogenous population.

We examined endothelial function with FMD, which is a simple noninvasive, harmless, accurate, and reproducible method that enables assessment of the vascular response to flow increase. FMD is currently the main method used to assess endothelial function and is convenient for clinical practice.[17]

Cikim *et al*.[1] were the first showed FMD values decreased in SHy, and our study showed the same finding. In that study, the patients include both exogenous and endogenous SHy. Yavuz *et al*. illustrated that TSH suppression therapy with levothyroxine leading to exogenous SHy may cause impaired endothelial function and decreased FMD.[18] However, another study demonstrated that flow-mediated endothelium-dependent vasodilation, as assessed by a noninvasive determinant of brachial FMD, increased in hyperthyroid patients.[19] This differences may be explained by the difference between subclinical and overt hyperthyroid condition. All the patients in that study were endogenous hyperthyroidism, and this was another dissimilarity between two studies.

Using ultrasound to measure IMT of the carotid artery is one of accepted method for detection of early atherosclerotic changes, which has been proven to be directly related to coronary artery disease.[14] However, we could not find any significant association between SHy and IMT. Cikim *et al*.[1] reported no significant differences in mean carotid IMT in a group of SHy patients compared to a euthyroid group. Cabral *et al*.[20] reported the same finding in SHy. However, the results are controversial in measuring IMT in subclinical hypothyroidism.[21-23] These results suggesting that subclinical hyperthyroidism and SHy is not associated with an increase in cardiovascular risk when assessed by carotid IMT.[23] There is not clear in thyroid dysfunction what the causative agent of endothelial damage is, but seems thyroid autoantibodies induce decreased endothelial NO synthesis or inflammation.[24]

This study also makes obvious that FMD values enhanced when hyperthyroid status was restored to euthyroid state; however, the FMD levels remained lower than those of controls. This finding is in accordance with previous studies showing that vascular reactivity in hyperthyroid state can be restored by either medical therapy or subtotal thyroidectomy.[25,26] Partial restoration of FMD when treating hyperthyroid patients may be due to increase of endothelium-derived hyperpolarizing factor in hyperthyroid patients, which cannot be corrected by treatment.[27] In our study, we illustrate that FMD changes are not related to hypothyroidism background because after reduce dose of levothyroxine, FMD became better than past.

Limitation of our study was that we did not compare the anti-thyroid peroxidase level in SHy before and after treatment. Therefore, we could not clarify the possible effect of inflammation in these findings.

CONCLUSION

Our study demonstrated that flow-mediated endothelium-dependent vasodilation, as assessed by a noninvasive determinant of brachial FMD, decreased in subclinical hyperthyroid patients which could be partially restored by treatment. These findings suggest that treatment of subclinical hyperthyroid state could improve endothelial dysfunction and at the end decreased the cardiovascular complications.

Acknowledgment

This study was funded by the Isfahan Endocrine and Metabolism Research Centre. We are grateful to all volunteer who participated in our study. We also wish to thank staff of Isfahan Endocrine and Metabolism Research Centre for the financial support of this study.

Financial support and sponsorship

Isfahan Endocrine and Metabolism Research Centre.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Cikim AS, Oflaz H, Ozbey N, Cikim K, Umman S, Meric M, *et al.* Evaluation of endothelial function in subclinical hypothyroidism and subclinical hyperthyroidism. Thyroid 2004;14:605-9.
2. Cooper DS. Approach to the patient with subclinical hyperthyroidism. Thyroid 2010;20:135-46.
3. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526-34.
4. Toft AD. Clinical practice. Subclinical hyperthyroidism. N Engl J Med 2001;345:512-6.
5. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501-9.
6. Abdu TA, Elhadd T, Pfeifer M, Clayton RN. Endothelial dysfunction in endocrine disease. Trends Endocrinol Metab 2001;12:257-65.
7. Shargorodsky M, Serov S, Gavish D, Leibovitz E, Harpaz D, Zimlichman R. Long-term thyrotropin-suppressive therapy with levothyroxine impairs small and large artery elasticity and increases left ventricular mass in patients with thyroid carcinoma. Thyroid 2006;16:381-6.
8. Burggraaf J, Lalezari S, Emeis JJ, Vischer UM, de Meyer PH, Pijl H, *et al.* Endothelial function in patients with hyperthyroidism before and after treatment with propranolol and thiamazol. Thyroid 2001;11:153-60.
9. Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007;116:1725-35.
10. Klein I, Laragh J, Brenner B, Kaplan N. Thyroid hormone and blood pressure regulation. Endocrine Mechanisms of Hypertension. New York: Raven Press; 1989.
11. Resnick LM, Laragh JH. Plasma renin activity in syndromes of thyroid hormone excess and deficiency. Life Sci 1982;30:585-6.
12. Palmeiro C, Davila MI, Bhat M, Frishman WH, Weiss IA. Subclinical hyperthyroidism and cardiovascular risk: Recommendations for treatment. Cardiol Rev 2013;21:300-8.
13. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation 2003;108:2054-9.
14. Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: A new tool for diagnosis and treatment of cardiovascular risk. J Hypertens 2002;20:159-69.
15. Gazdag A, Nagy EV, Burman KD, Paragh G, Jenei Z. Improved endothelial function and lipid profile compensate for impaired hemostatic and inflammatory status in iatrogenic chronic subclinical hyperthyroidism of thyroid cancer patients on L-t4 therapy. Exp Clin Endocrinol Diabetes 2010;118:381-7.
16. Javanmard SH, Sonbolestan SA, Heshmat-Ghahdarijani K, Saadatnia M, Sonbolestan SA. Enalapril improves endothelial function in patients with migraine: A randomized, double-blind, placebo-controlled trial. J Res Med Sci 2011;16:26-32.
17. Faulx MD, Wright AT, Hoit BD. Detection of endothelial dysfunction with brachial artery ultrasound scanning. Am Heart J 2003;145:943-51.
18. Yavuz DG, Yazici D, Toprak A, Deyneli O, Aydin H, Yüksel M, *et al.* Exogenous subclinical hyperthyroidism impairs endothelial function in nodular goiter patients. Thyroid 2008;18:395-400.
19. Ho WJ, Chen ST, Tsay PK, Wang CL, Hsu TS, Kuo CT, *et al.* Enhancement of endothelium-dependent flow-mediated vasodilation in hyperthyroidism. Clin Endocrinol (Oxf) 2007;67:505-11.
20. Cabral MD, Teixeira PF, Silva NA, Morais FF, Soares DV, Salles E, *et al.* Normal flow-mediated vasodilatation of the brachial artery and carotid artery intima-media thickness in subclinical hypothyroidism. Braz J Med Biol Res 2009;42:426-32.
21. Monzani F, Caraccio N, Kozàkowà M, Dardano A, Vittone F, Virdis A, *et al.* Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: A double-blind, placebo-controlled study. J Clin Endocrinol Metab 2004;89:2099-106.
22. Völzke H, Robinson DM, Schminke U, Lüdemann J, Rettig R, Felix SB, *et al.* Thyroid function and carotid wall thickness. J Clin Endocrinol Metab 2004;89:2145-9.
23. Almeida CA, Teixeira Pde F, Soares DV, Cabral MD, Costa SM, Salles EF, *et al.* Carotid intima-media thickness as a marker of cardiovascular risk in patients with subclinical hypothyroidism. Arq Bras Endocrinol Metabol 2007;51:472-7.
24. Taddei S, Caraccio N, Virdis A, Dardano A, Versari D, Ghiadoni L, *et al.* Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis. J Clin Endocrinol Metab 2006;91:5076-82.
25. Napoli R, Biondi B, Guardasole V, Matarazzo M, Pardo F, Angelini V, *et al.* Impact of hyperthyroidism and its correction on vascular reactivity in humans. Circulation 2001;104:3076-80.
26. Guang-da X, Hong-yan C, Xian-mei Z. Changes in endothelium-dependent arterial dilation before and after subtotal thyroidectomy in subjects with hyperthyroidism. Clin Endocrinol (Oxf) 2004;61:400-4.
27. Ortega J, Vila JM, Mauricio MD, Segarra G, Medina P, Martínez-León JB, *et al.* Nitric oxide mediates abnormal responsiveness of thyroid arteries in methimazole-treated patients. Eur J Endocrinol 2005;152:551-6.

To,
The Editor

Covering Letter

Submission of Manuscript for publication

Dear Sir,

We intend to publish an article entitled

_____

in your journal.
On behalf of all the contributors I will act and guarantor and will correspond with the journal from this point onward.

Prior presentation of the data reported in this manuscript:

Organisation
Place
Date

We have done sufficient work in the field to justify authorship for this manuscript.

We hereby transfer, assign, or otherwise convey all copyright ownership, including any and all rights incidental thereto, exclusively to the journal, in the event that such work is published by the journal.

Thank you,
Yours' sincerely,

Name of corresponding contributor

Signature

Title of the manuscript:

Type of manuscript:
Running title:
Contributors:

	First name	Middle name initial	Last name	Highest academic degree	Names of departments and institutions (including city and state)	Email addresses
1						
2						
3						
4						
5						
6						

Corresponding Author:
Name:
Address:
Phone numbers:
Facsimile numbers:
E-mail address:

Total number of pages:
Total number of tables:
Total number of figures:
Total number of supplementary files:
Word counts: For abstract: For the text:

Acknowledgement:

Conflict of interest:

Financial Support:

Contributors' form

Contribution details (to be ticked marked as applicable):

	Contributor 1	Contributor 2	Contributor 3	Contributor 4	Contributor 5	Contributor 6
Concepts						
Design						
Definition of intellectual content						
Literature search						
Clinical studies						
Experimental studies						
Data acquisition						
Data analysis						
Statistical analysis						
Manuscript preparation						
Manuscript editing						
Manuscript review						
Guarantor						