TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 1751-1756

doi:10.3906/sag-1610-139

Evaluation of ambulatory arterial stiffness index in hyperthyroidism

Özlem TURHAN İYİDİR[1]*, Mehmet Muhittin YALÇIN[1], Alev EROĞLU ALTINOVA[1], Emre ARSLAN[1], Bahar UNCU[2], Ceyla KONCA DEĞERTEKİN[1], Füsun BALOŞ TÖRÜNER[1]

[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Gazi University, Ankara, Turkey
[2]Department of Internal Medicine, Faculty of Medicine, Gazi University, Ankara, Turkey

Received: 07.11.2016 • **Accepted/Published Online:** 06.08.2017 • **Final Version:** 19.12.2017

Background/aim: Hyperthyroidism causes hemodynamic changes that are associated with adverse cardiovascular outcomes. Twenty-four-hour ambulatory blood pressure monitoring recordings provide us with some essential data: BP variability and ambulatory arterial stiffness index (AASI). In this study, we aimed to investigate AASI and short-term BP variability in both overt and subclinical hyperthyroidism and their relationship with thyroid hormones.

Materials and methods: We enrolled 36 patients with subclinical hyperthyroidism, 23 patients with overt hyperthyroidism, and 25 healthy euthyroid controls. ABPM recording was performed for 24 h for all patients.

Results: There were no statistically significant differences among the overt hyperthyroidism, subclinical hyperthyroidism, and control groups in terms of AASI (0.43 ± 0.15, 0.38 ± 0.12, 0.42 ± 0.13, respectively; P = 0.315). Variability of diastolic BP was significantly higher in patients with overt hyperthyroidism than in patients with subclinical hyperthyroidism (14.8 ± 2.6 vs. 12.8 ± 2.5%, P = 0.023). There were significant positive correlations between AASI and fT3 (r = 0.246, P = 0.02) and fT4 (r = 0.219, P = 0.04) while TSH was not correlated with AASI (r = 0.023, P = 0.838). After adjusting for confounders, age, 24-h systolic and diastolic BP, variability of systolic and diastolic BP, and fT4 were independent predictors of AASI (r^2 = 0.460, P < 0.001).

Conclusion: Although AASI did not differ between overt and subclinical hyperthyroidism, there was a positive relationship between AASI and free thyroid hormone levels. Furthermore, short-term BP variability was higher in overt hyperthyroidism than in subclinical hyperthyroidism.

Key words: Ambulatory arterial stiffness index, blood pressure variability, hyperthyroidism

1. Introduction

Thyroid hormones interact with endothelial function, vascular reactivity, renal hemodynamics, and the renin–angiotensin system (1). Thus, thyroid disorders cause certain hemodynamic changes leading to elevated blood pressure (BP) (2). Overt hyperthyroidism, whether endogenous or exogenous in origin, is associated with increased cardiac output, increased resting heart rate, contractility, ejection fraction, and blood volume with decreased systemic vascular resistance (3). Higher heart rate, frequent atrial premature beats, increased prevalence of atrial fibrillation, increased left ventricular mass, and diastolic dysfunction are also reported in subclinical hyperthyroidism. Several studies showed that there is an association between overt and subclinical hyperthyroidism and increased arterial stiffness, as well as impaired vascular elasticity (4,5).

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is a noninvasive way of reviewing arterial changes associated with cardiovascular risk. Ambulatory arterial stiffness index (AASI) is a parameter based on the relationship between diastolic and systolic blood pressure derived from ABPM recordings and was recently proposed as a relatively easy way to measure arterial stiffness (6). Although there is quite some debate about the use of AASI as a marker for arterial stiffness, recent prospective studies showed that elevated AASI is an independent predictor for cardiovascular mortality and stroke and is a valuable tool for cardiovascular risk stratification (7,8). Short-term blood pressure variability is defined as the standard deviation or coefficient variation from the mean BP in 24-h ABPM recordings (9). Variability may reflect alterations in cardiovascular regulatory mechanisms, which in turn may also affect cardiovascular prognosis (10).

In this study, we aimed to investigate how AASI and BP variability change in patients with overt and subclinical hyperthyroidism.

* Correspondence: ozturhan78@hotmail.com

2. Methods

2.1. Study groups

We enrolled 59 patients with hyperthyroidism and 25 healthy euthyroid controls in the study. None of the participants had a medical history of chronic disease such as hypertension, diabetes mellitus, chronic renal failure, chronic hepatic disease, and cardiovascular diseases. The hyperthyroid group included 36 patients with subclinical hyperthyroidism and 23 patients with overt hyperthyroidism. Overt hyperthyroidism was defined as suppressed TSH with high free fT3 (fT3) and/or free T4 (fT4) levels, which was caused by Graves' disease in all cases. Subclinical hyperthyroidism was defined as suppressed TSH with normal fT3 and fT4 levels on two occasions in 6 months. Patients with both endogenous and exogenous subclinical hyperthyroidism were included in the study. The etiologies of endogenous subclinical hyperthyroidism were toxic adenoma or toxic multinodular goiter. For exogenous subclinical hyperthyroidism, patients with differentiated thyroid cancer under TSH suppression due to levothyroxine therapy were included. Among the 23 patients with subclinical hyperthyroidism 12 had toxic adenoma or toxic multinodular goiter and 11 had exogenous subclinical hyperthyroidism due to levothyroxine treatment. Median duration of levothyroxine treatment of the patients with differentiated thyroid cancer was 6 (2–8) years and the mean daily dose of levothyroxine was 125 μg/day.

The study protocol was approved by the ethics committee of Gazi University, and the study was carried out in accordance with the principles of the Declaration of Helsinki. All subjects gave their written informed consent before participating in this study.

2.2. Laboratory measurements

Serum TSH, fT3 and fT4 concentrations were measured with chemiluminescent immunoassay on an automatic analyzer (Architect, Abbott Diagnostics, Abbott Park, IL, USA). Normal ranges were as follows: fT3 (1.71–3.71 pg/mL), fT4 (0.76–1.89 ng/dL), and TSH (0.35–4.94 mIU/L).

2.3. Measurement of BP variability and AASI

Office BP was obtained by calculating the mean of two separate measurements with at least a 5-min interval. BP was measured in every patient during the clinic visit by the same nurse using a mercury sphygmomanometer, on the left arm, after 5 min of rest. ABPM recording was performed for 24 h using Spacelabs model 90207 monitors (Issaquah, WA, USA), on a day of standard activity, with an adequate cuff size of the patient's arm. The records of readings considered to be valid were ≥80% of the total. The monitor was programmed for obtaining blood pressure measurements every 20 min during the waking period and every 30 min during the resting period. Individual correction was made for the waking and sleeping hours as reported by the patient.

Systolic and diastolic BP variability were expressed by the coefficient of variation (CV) of systolic or diastolic measurements, defined by using relative changes (CV = 100 × s.d./mean). AASI is defined as 1 – (diastolic-on-systolic slope), wherein the slope was determined from a DBP vs. SBP plot by a standard regression procedure (6).

Nocturnal dipping (%) was defined as the percentage decrease in nocturnal systolic BP compared with daytime systolic BP. When patients showed nocturnal dipping of less than 10%, they were defined as "nondippers".

2.4. Statistical analysis

Analyses were performed using SPSS version 15.0 for Windows (SPSS, Chicago, IL, USA) and GraphPad Prism software version 6.0 (GraphPad, San Diego, CA, USA). Continuous data were presented as means ± standard deviation or median [minimum–maximum], as appropriate. Chi-square (categorical variables) and ANOVA/Kruskal–Wallis (continuous variables) tests were used to assess differences between groups. Post hoc comparisons were carried out using the Mann–Whitney U test for nonparametric variables and Tukey's test for parametric variables. Bonferroni correction was applied for multiple comparisons of nonparametric variables. Pearson correlation analysis was used to test for correlation of normal variables considered to be associated with AASI, whereas Spearman correlation analysis was used for variables not showing a normal distribution. Multiple linear regression analysis was used to determine predictors among risk factors considered to be related to AASI in the entire population. $P < 0.05$ was considered to be statistically significant.

3. Results

The demographic, biochemical, and anthropometric characteristics of the patients included in the study are given in Table 1. Mean age of all study subjects was 45.2 ± 10.5 years and 61 (72.6%) of the participants were women. Patients with overt hyperthyroidism were younger than patients with subclinical hyperthyroidism and controls (38.5 ± 9.7 vs. 47.8 ± 10.2 and 47.7 ± 9.0 years, respectively; $P = 0.001$) (Table 1). The groups were similar in terms of sex distribution ($P = 0.295$) (Table 1).

In patients with overt and subclinical hyperthyroidism TSH levels were lower and fT4 levels were higher compared with the control subjects ($P < 0.001$ for TSH; $P < 0.001$ for fT4), (Table 1). Serum fT3 levels were significantly higher in patients with overt hyperthyroidism compared to those with subclinical hyperthyroidism and the controls ($P < 0.001$) (Table 1).

Heart rate of the patients with overt hyperthyroidism was significantly higher than that of patients with

Table 1. Demographic, ambulatory blood pressure monitoring, and biochemical characteristics of the study subjects.

	Ohyper (n = 23)	Shyper (n = 36)	Control (n = 25)	P
Age (years)	38.5 ± 9.8	47.8 ± 10.2	47.8 ± 9	0.001[a,b]
Sex (male) [n, (%)]	8 (34.8)	11(30.6)	4 (16)	0.295
Heart rate (beats/min)	91 ± 12	76 ± 7	73 ± 6	<0.001[a,b]
Office systolic BP (mmHg)	130.3 ± 10.3	120.3 ± 9.5	123.6 ± 10.4	0.002[a]
Office diastolic BP (mmHg)	81.0 ± 9.2	76.4 ± 6.4	77.1 ± 8.8	0.096
24-h systolic BP (mmHg)	125.4 ± 7.7	117.9 ± 9.0	119.0 ± 9.0	0.005[a,b]
24-h diastolic BP (mmHg)	72.2 ± 5.6	73.4 ± 6.1	72.2 ± 5.6	0.592
24-h systolic CV(%)	9.7 ± 2.0	9.2 ± 1.6	10.3 ± 2.0	0.077
24-h diastolic CV (%)	14.8 ± 2.6	12.8 ± 2.5	14.1 ± 3.3	0.023[a]
Daytime systolic BP (mmHg)	128.0 ± 8.7	118.5 ± 8	122.6 ± 9.4	0.001[a]
Daytime diastolic BP (mmHg)	75.2 ± 6.4	76.2 ± 10.0	77.5 ± 7.3	0.145
Night-time systolic BP (mmHg)	119.0 ± 7.2	108.5 ± 11.1	112.0 ± 10.2	0.001[a,b]
Night-time diastolic BP (mmHg)	66.4 ± 5.9	66.4 ± 5.8	67.0 ± 9.3	0.838
Nondipper [n, (%)]	18 (78)	24 (75)	18 (72)	0.882
AASI	0.43 ± 0.15	0.38 ± 0.12	0.42 ± 0.13	0.315
fT3 (pg/mL)	14.2 ± 7.64	3.09 ± 0.33	2.94 ± 0.28	<0.001[a,b]
fT4 (ng/mL)[ǂ]	3.39 (1.57–7.77)	1.38 (0.38–1.70)	1.17 (0.90–1.59)	<0.001[a,b,c]
TSH (mIU/L)[ǂ]	0.005 (0.005–0.11)	0.11 (0.001–0.34)	1.32 (0.47–3.79)	<0.001[a,b,c]

ǂ: Data are given as median (minimum–maximum) or as mean ± SD, Ohyper: overt hyperthyroidism, Shyper: subclinical hyperthyroidism, BP: blood pressure, CV: coefficient of variation, AASI: ambulatory arterial stiffness index, fT4: free T4, fT3: free T3, TSH: thyroid stimulating hormone

a: Ohyper vs. shyper by the appropriate statistical test.

b: Ohyper vs. control by the appropriate statistical test.

c: Shyper vs. control by the appropriate statistical test.

subclinical hyperthyroidism and the controls (91 ± 12 vs. 76 ± 7 and 73 ± 6/min, respectively; P < 0.001).

Office systolic BP measurements were significantly higher in patients with overt hyperthyroidism than in patients with subclinical hyperthyroidism and the controls (130.3 ± 10.3 vs. 120.3 ± 9.5 and 123.6 ± 10.4 mmHg, respectively; P = 0.002). Twenty-four-hour systolic BP measurements in ABPM recordings were significantly higher in patients with overt hyperthyroidism compared with patients with subclinical hyperthyroidism and the controls (125.4 ± 7.7 vs. 117.9 ± 9.0 and 119.0 ± 9.0 mmHg, respectively; P = 0.005). Night-time systolic BPs in ABPM recordings were significantly higher in patients with overt hyperthyroidism than in patients with subclinical hyperthyroidism and the controls (119.0 ± 7.2 vs. 108.5 ± 11.1 and 112.0 ± 10.2 mmHg respectively; P = 0.001). Day-time systolic BPs in ABPM recordings were significantly higher in patients with overt hyperthyroidism than in patients with subclinical hyperthyroidism (128.0 ± 8.7 vs. 118.5 ± 8 mmHg, P = 0.001). However, there was no significant difference between patients with overt hyperthyroidism and the control group in terms of day-time systolic BPs in ABPM recordings (128.0 ± 8.7 vs. 122.6 ± 9.4 mmHg, P = 0.08).

Variability of diastolic BP, as expressed by 24-h diastolic CV, was significantly higher in patients with overt hyperthyroidism than in patients with subclinical hyperthyroidism (14.8 ± 2.6 vs. 12.8 ± 2.5%, P = 0.023).

There were no statistically significant differences among the overt hyperthyroidism, subclinical hyperthyroidism, and control groups in terms of AASI (0.43 ± 0.15, 0.38 ± 0.12, 0.42 ± 0.13, respectively; P = 0.315). After adjustment for age, the groups were still similar for AASI (P = 0.104).

When the whole group was analyzed, there were significant positive correlations between AASI and fT3 (r = 0.246, P = 0.02) and fT4 (r = 0.219, P = 0.04), while TSH was not correlated with AASI (r = 0.023, P = 0.838). After adjusting for confounders, age, 24-hsystolic and diastolic BP, variability of systolic and diastolic BP (24-h systolic and diastolic CV), and fT4 were independent predictors of AASI (r^2 = 0.460, P < 0.001). Table 2 shows the results of multiple regression analysis.

Table 2. Independent predictors of AASI in a multiple regression analysis best fitting model ($R^2 = 0.460$).

	β	P
Age (years)	0.003	0.044
Sex	0.039	0.182
24-h systolic BP (mmHg)	0.008	<0.001
24-h diastolic BP (mmHg)	–0.012	<0.001
24-h systolic CV (%)	0.040	0.001
24-h diastolic CV (%)	–0.044	<0.001
Nondipper	–0.009	0.758
fT4 (ng/mL)	0.020	0.045

BP: blood pressure, CV: coefficient of variation, AASI: ambulatory arterial stiffness index, fT4: free T4

4. Discussion

In this study, we found a significant relationship between AASI and free thyroid hormones; however, AASI did not differ between patients with overt and subclinical hyperthyroidism and control subjects. Variability in diastolic BP was higher in patients with overt hyperthyroidism than in patients with subclinical hyperthyroidism in our study.

Thyroid disorders are related to increased prevalence of cardiovascular disease and atherosclerosis (1). Overt hyperthyroidism is a risk factor for atrial fibrillation, stroke, and cardiovascular mortality (11). Arterial stiffness is an early and important risk factor for development of cardiovascular diseases (12). Some studies have investigated the possible effects of thyroid hormone excess on arterial stiffness with different measurement methods (13). However, the association between hyperthyroidism and arterial stiffness is still not clear due to controversial results of the previous studies in the literature. Palmieri et al. found that arterial stiffness was increased in overt hyperthyroidism (14). Similarly, aortic stiffness was reported to be increased in patients with exogenous subclinical hyperthyroidism (5). Inaba et al. showed a significant decrease in stiffness index in the carotid artery after maintaining euthyroid state in patients with overt hyperthyroidism, but this study did not include a control group (15). In contrast, Obuobie et al. showed decreased augmentation of central arterial pressure and reduced arterial stiffness in untreated thyrotoxicosis (16). A cross sectional study found that stiffness of the common carotid artery, which was calculated with a different method from ours, was not different in patients with hyperthyroid Graves' disease compared to euthyroid controls, which is in line with our findings. In that study, there were strong correlations between arterial stiffness and thyroid hormone levels, which is also similar to our results (17). The distinctive feature of our study is that we also included patients with subclinical hyperthyroidism and found that these patients also had AASI similar to the control group. To the best of our knowledge, this is the first study that investigated AASI in both overt and subclinical hyperthyroid states. Regarding the possible mechanisms for similar AASI in hyperthyroid and control groups, Kips et al. found that both vascular resistance and heart rate were inversely related to AASI (18). Hyperthyroidism increases heart rate and is associated with decreased systemic vascular resistance. These opposing mechanisms may have a confounding effect on AASI and might explain the lack of difference in terms of AASI between overt and subclinical hyperthyroid and control groups in our study.

In our study, we also found significant positive correlations between AASI and free thyroid hormones. Our data are consistent with a previous study by Delitala et al., who found a relationship between fT4 and pulse wave velocity but not with TSH (19). These findings, taken together, suggest that excess thyroid hormones may have some unfavorable effects on arterial stiffness in the long term. Future studies with larger patient groups on this topic are needed.

Age is a major determinant of arterial stiffness in large elastic arteries and stiffness increases especially after the age of 55 (20). The patients with overt hyperthyroidism in our study were younger due to Graves' disease, which peaks in the third to fourth decade of life (21). Although they were younger than subclinical hyperthyroid patients and euthyroid controls, we did not observe any difference in terms of AASI between the groups. However, there was a positive correlation between fT3 and fT4 and AASI in patients with overt hyperthyroidism despite the younger age of these patients.

BP variability, expressed as CV, was an independent predictor of AASI in our study. This result suggests that AASI may not only measure arterial stiffness but may also represent BP variability. Further studies are needed to evaluate the alteration of BP variability and AASI after maintaining euthyroidism.

Our results also showed that BP measurements obtained instantly at the office, by ABPM throughout the 24 h, and BP variability calculated through ABPM are higher in overt hyperthyroidism compared to subclinical hyperthyroidism.

Short-term BP variability is estimated from ABPM recordings by calculating 24 h BP SD or CV (22). Variability of diastolic BP was higher in patients with overt hyperthyroidism than in patients with subclinical hyperthyroidism in our study. The pathophysiological mechanisms of BP variability in hyperthyroidism remain unclear. Increased short-term BP variability in

overt hyperthyroidism might be explained by increased sympathetic nerve activity and decreased systemic vascular resistance.

There are scarce data about 24-h BP recordings in patients with hyperthyroidism. A previous study showed that the average 24-h BP measurements in patients with hyperthyroidism were similar to those in euthyroid subjects (23). Iglesias et al. reported higher systolic BP in patients with overt hyperthyroidism compared with euthyroid controls and systolic BP decreased after normalization of thyroid hormone levels (24). In our study, in accordance with previous studies, overt hyperthyroid patients had higher systolic BP than euthyroid subjects whereas the groups were similar for diastolic BP throughout the 24-h period. We could not find any difference between patients with subclinical hyperthyroidism and control subjects in terms of systolic and diastolic BP. Our result is consistent with a metaanalysis by Cai et al., which indicated that subclinical hyperthyroidism is not associated with increased BP (25). These findings taken together suggest that blood pressure alterations are more noticeable in overt hyperthyroidism.

The major limitations of our study are the relatively small sample size and the heterogeneity of the etiologies of the patients with subclinical hyperthyroidism.

In conclusion, our study showed that while there was a positive relationship between AASI and free thyroid hormones, AASI did not differ between overt and subclinical hyperthyroidism and short-term BP variability was higher in overt hyperthyroidism than in subclinical hyperthyroidism. Further studies are needed to enlighten the possible relation between arterial stiffness and excess thyroid hormones. Larger prospective studies investigating the alteration in BP variability and AASI after maintaining euthyroidism may potentially broaden our understandings about the vascular effects of thyroid hormones.

References

1. Danzi S, Klein I. Thyroid disease and the cardiovascular system. Endocrinol Metab Clin North Am 2014; 43: 517-528.
2. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344: 501-509.
3. Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007; 116: 1725-1735.
4. 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: 381-386.
5. Gazdag A, Nagy EV, Erdei A, Bodor M, Berta E, Szabo Z, Jenei Z. Aortic stiffness and left ventricular function in patients with differentiated thyroid cancer. J Endocrinol Invest 2015; 38: 133-142.
6. Li Y, Wang JG, Dolan E, Gao PJ, Guo HF, Nawrot T, Stanton AV, Zhu DL, O'Brien E, Staessen JA. Ambulatory arterial stiffness index derived from 24-hour ambulatory blood pressure monitoring. Hypertension 2006; 47: 359-364.
7. Kikuya M, Staessen JA, Ohkubo T, Thijs L, Metoki H, Asayama K, Obara T, Inoue R, Li Y, Dolan E et al. Ambulatory arterial stiffness index and 24-hour ambulatory pulse pressure as predictors of mortality in Ohasama, Japan. Stroke 2007; 38: 1161-1166.
8. Dolan E, Thijs L, Li Y, Atkins N, McCormack P, McClory S, O'Brien E, Staessen JA, Stanton AV. Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study. Hypertension 2006; 47: 365-370.
9. Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, Grassi G, di Rienzo M, Pedotti A, Zanchetti A. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. Circ Res 1983; 53: 96-104.
10. Parati G, Ochoa JE, Lombardi C, Bilo G. Blood pressure variability: assessment, predictive value, and potential as a therapeutic target. Curr Hypertens Rep 2015; 17: 537.
11. Grais IM, Sowers JR. Thyroid and the heart. Am J Med 2014; 127: 691-698.
12. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27: 2588-2605.
13. Kollias A, Stergiou GS, Dolan E, O'Brien E. Ambulatory arterial stiffness index: a systematic review and meta-analysis. Atherosclerosis 2012; 224: 291-301.
14. Palmieri EA, Fazio S, Palmieri V, Lombardi G, Biondi B. Myocardial contractility and total arterial stiffness in patients with overt hyperthyroidism: acute effects of beta1-adrenergic blockade. Eur J Endocrinol 2004; 150: 757-762.
15. Inaba M, Henmi Y, Kumeda Y, Ueda M, Nagata M, Emoto M, Ishikawa T, Ishimura E, Nishizawa Y. Increased stiffness in common carotid artery in hyperthyroid Graves' disease patients. Biomed Pharmacother 2002; 56: 241-246.
16. Obuobie K, Smith J, John R, Davies JS, Lazarus JH. The effects of thyrotoxicosis and its treatment on central arterial stiffness. Eur J Endocrinol 2002; 147: 35-40.
17. Czarkowski M, Hilgertner L, Powalowski T, Radomski D. The stiffness of the common carotid artery in patients with Graves' disease. Int Angiol 2002; 21: 152-157.
18. Kips JG, Vermeersch SJ, Reymond P, Boutouyrie P, Stergiopulos N, Laurent S, Van Bortel LM, Segers P. Ambulatory arterial stiffness index does not accurately assess arterial stiffness. J Hypertens 2012; 30: 574-580.

19. Delitala AP, Orru M, Filigheddu F, Pilia MG, Delitala G, Ganau A, Saba PS, Decandia F, Scuteri A, Marongiu M et al. Serum free thyroxine levels are positively associated with arterial stiffness in the SardiNIA study. Clin Endocrinol (Oxf) 2015; 82: 592-597.

20. Wu CF, Liu PY, Wu TJ, Hung Y, Yang SP, Lin GM. Therapeutic modification of arterial stiffness: an update and comprehensive review. World J Cardiol 2015; 7: 742-753.

21. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull 2011; 99: 39-51.

22. di Rienzo M, Grassi G, Pedotti A, Mancia G. Continuous vs intermittent blood pressure measurements in estimating 24-hour average blood pressure. Hypertension 1983; 5: 264-269.

23. Kohno I, Iwasaki H, Okutani M, Mochizuki Y, Sano S, Satoh Y, Ishihara T, Ishii H, Ijiri H, Komori S et al. Circadian blood pressure and heart rate profiles in normotensive patients with mild hyperthyroidism. Chronobiol Int 1998; 15: 337-347.

24. Iglesias P, Acosta M, Sanchez R, Fernandez-Reyes MJ, Mon C, Diez JJ. Ambulatory blood pressure monitoring in patients with hyperthyroidism before and after control of thyroid function. Clin Endocrinol (Oxf) 2005; 63: 66-72.

25. Dorr M, Ittermann T, Aumann N, Obst A, Reffelmann T, Nauck M, Wallaschofski H, Felix SB, Volzke H. Subclinical hyperthyroidism is not associated with progression of cardiac mass and development of left ventricular hypertrophy in middle-aged and older subjects: results from a 5-year follow-up. Clin Endocrinol (Oxf) 2010; 73: 821-826.