Thyroid Function in Patients With a Fontan Circulation

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In this study, we tested our hypothesis that thyroid function is impaired and contributes to perturbed hemodynamics in patients after Fontan operation. Cardiac catheterization and blood tests for thyroid function were performed in 37 patients who underwent a Fontan operation. Among them, 12 patients (33%) had subclinical thyroid dysfunction with an elevated thyroid-stimulating hormone level despite normal thyroxine levels. Thyroid-stimulating hormone levels were significantly correlated with central venous pressure ($p < 0.01$, $R^2 = 0.3$), and patients with subclinical hypothyroidism showed significantly elevated γ-glutamyltransferase level, an indicator of liver congestion, compared with the other patients (125.6 ± 12.2 vs 67.6 ± 4.6 IU/L, $p < 0.01$). In addition, the levels of free triiodothyronine, an effective thyroid hormone, were significantly lower in patients with subclinical hypothyroidism than in those with normal thyroid function (3.1 ± 0.1 vs 3.5 ± 0.1 pg/dl, $p < 0.01$). The free triiodothyronine level was significantly and negatively correlated with the relaxation time constant ($p = 0.03$) and brain natriuretic hormone ($p < 0.01$) level and positively correlated with the cardiac index ($p = 0.04$). In conclusion, venous congestion in Fontan patients may cause thyroid dysfunction, which can be responsible for decreased ventricular function and cardiac output in Fontan patients. Thus, thyroid function should be routinely monitored after Fontan surgery. **(Am J Cardiol 2019;123:979−983)**

Fontan circulation is characterized by an increase in central venous pressure (CVP) and a decrease in cardiac output caused by the absence of the pulmonary ventricle.[1,2] Recent studies regarding the long-term outcomes of patients with Fontan circulation have emphasized that such hemodynamic characteristics, particularly an elevated CVP or venous congestion, cause various organ dysfunctions including the liver, kidney, intestine, airway, and possibly the brain.[3,4] This fact raises the possibility that Fontan hemodynamics may also have adverse effects on the thyroid gland, causing thyroid function impairment. Because the thyroid hormones play important roles in maintaining the cardiovascular function,[5−7] thyroid dysfunction may in turn adversely affect the hemodynamics of Fontan circulation, forming a vicious cycle of Fontan pathophysiology. In this study, we hypothesized that increased CVP in Fontan circulation is associated with decreased thyroid function and that the hemodynamic characteristics of the Fontan circulation is partly attributed to the decreased thyroid function.

Methods

A retrospective analysis was conducted on the hemodynamic parameters and thyroid function of 38 consecutive patients who underwent cardiac catheterization after a Fontan operation. One patient treated with amiodarone was excluded from the analysis. All patients underwent cardiac catheterization under general anesthesia. Ventricular and vascular pressures were measured using a high-fidelity pressure transducer mounted on a 0.014-inch guidewire. The cardiac index (CI) was determined using the Fick method, and the circulatory blood volume was determined by a dye dilution technique (DDG analyzer, Nihon Kohden, Japan).[8] During cardiac catheterization, blood samples were taken from the inferior vena cava to measure the serum thyroid hormone levels, including the thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). In addition, we measured the serum levels of aldosterone and brain natriuretic hormone as heart failure-related hormones; gamma-glutamyltransferase (γGTP) and total bilirubin as indicators of liver congestion; hyaluronic acid as a measure of tissue fibrosis; and creatinine and cystatin C as markers of renal function. Vascular endothelial function was also evaluated by measurement of the serum levels of von Willebrand factor[9] and flow-mediated vasodilation (FMD). Cardiac catheterization studies were performed after obtaining a written informed consent from the patients' parents. The study was approved by the institutional review board on clinical investigation (no. 1547 at Saitama Medical Center).

Data are presented as mean ± standard deviation (range). Data comparison between the 2 groups was performed using the Wilcoxon rank test, whereas relations

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Table 1
Characteristics of the patients

	All patients (n = 35)	Subclinical hypothyroidism (n = 12)	Normal thyroid (n = 23)	p value
Sex, male/female	21/14	6/6	15/8	
Age (years)	8.0 ± 3.9	7.0 ± 3.4	8.3 ± 4.3	0.4
Interval from Glenn (years)	6.1 ± 3.2	6.1 ± 3.3	6.0 ± 3.2	1.0
Interval from Fontan (years)	5.2 ± 4.0	4.5 ± 3.8	5.5 ± 4.3	0.4
Diagnosis				
Hypoplastic left heart syndrome	5	3	2	
Right dominant single ventricle	15	4	11	
Pulmonary atresia with intact ventricular septum	3	1	2	
Tricuspid atresia	3	1	2	
Double outlet of the right ventricle	8	3	5	
Asplenia	7	2	5	
Polysplenia	2	1	1	

between 2 parameters were analyzed using Pearson's correlation analysis. The correlations between hemodynamics and thyroid hormones were tested using univariate and multivariate linear regression analyses. A p value <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software for Windows (ver. 24; IBM Company, Chicago, Illinois).

Results

The patients' demographic data and underlying cardiac diseases are summarized in Table 1. None of the patients had chromosome anomaly (21 trisomy and 22q11.2 deletion syndrome). Table 2 shows the hemodynamic and laboratory data and FMD results.

As presented in Table 2, the FT4 (1.7 ± 0.31 pg/ml) and FT3 (3.33±0.55 pg/ml) levels were generally within the normal range, whereas the TSH level (5.56 ± 3.9 IU/L) was higher than the normal upper limit of 5 mIU/L. None of the patients had overt hyper- and/or hypothyroidism represented by abnormal FT4 and TSH levels; however, 12 patients had subclinical thyroid dysfunction with an elevated TSH level (>5 mIU/L) despite normal FT4 level.

Data comparison between patients with subclinical hypothyroidism (SCH) and normal thyroid function are also presented in Tables 1 and 2. CVP was significantly higher in patients with SCH than those with normal thyroid function (14.6 ± 4.4 vs 10.6 ± 3.0, p = 0.04), and the TSH levels were significantly correlated with CVP (Figure 1, p <0.01, $R^2 = 0.3$). In multivariate regression analysis, the Fontan hemodynamic parameters (CVP, CI, and heart rate) were included as independent variables and CVP remained a significant determinant of TSH level (p = 0.036). Consistent with these results, patients with SCH showed significantly elevated γGTP level, an indicator of liver congestion, compared with the other patients (125.6 ± 12.2 vs 67.6 ± 4.6 IU/L, p <0.01). The γGTP levels were positively correlated with the TSH levels (p <0.05). In addition, increased circulatory blood volume (p <0.05) and decreased hemoglobin levels (p <0.05) were significantly associated with elevated TSH levels.

FMD level was significantly lower in patients with SCH than in patients with normal thyroid (Table 2) and was negatively correlated with TSH levels ($R^2 = 0.23$, p = 0.03).

As shown in Figure 2, among the hemodynamic variables of Fontan circulation, FT3 level was significantly and positively correlated with CI (p = 0.04, $R^2 = 0.3$) and negatively correlated with the relaxation time constant (p = 0.04, $R^2 = 0.55$) and brain natriuretic hormone level (p <0.01).

Table 2
Hemodynamic and laboratory data

	All patients	Subclinical hypothyroidism	Normal thyroid	p value
Thyroid stimulation hormone (IU/L)	5.6 ± 3.9	8.7 ± 3.8	3.0 ± 1.3	<0.01
Free triiodothyronine (pg/ml)	3.3 ± 0.55	3.1 ± 0.56	3.5 ± 0.47	<0.01
Free thyroxine (ng/dl)	1.7 ± 0.31	1.6 ± 0.27	1.87 ± 0.33	0.20
Cardiac index (L/min/m^2)	3.3 ± 1.1	3.3 ± 1.3	3.3 ± 1.0	0.98
End-diastolic pressure (mm Hg)	7.8 ± 2.5	8.6 ± 3.0	7.5 ± 2.1	0.38
Tau (ms)	50.0 ± 22.7	52.1 ± 32.8	48.6 ± 14.0	0.40
Aldosterone (ng/dl)	444.5 ± 721.7	655.1 ± 998.9	336.1 ± 509.2	0.37
Gamma-glutamyltransferase (mg/dl)	87.7 ± 69.1	119.6 ± 86.9	60.8 ± 31.0	<0.01
Total-bilirubin (mg/dl)	0.83 ± 0.62	0.84 ± 0.73	0.82 ± 0.52	0.98
Hyaluronic acid (mg/dl)	33.0 ± 21.4	35.0 ± 22.4	32.0 ± 21.2	0.80
Cystatin C (mg/dl)	0.79 ± 0.16	0.77 ±0.15	0.82 ± 0.17	0.74
Brain natriuretic hormone (pg/ml)	21.9 ± 22.2	24.3 ± 19.8	20.1 ± 24.0	<0.01
von Willebrand factor (%)	98.1 ± 39.4	92.2 ± 15.8	101.1 ± 47.1	0.68

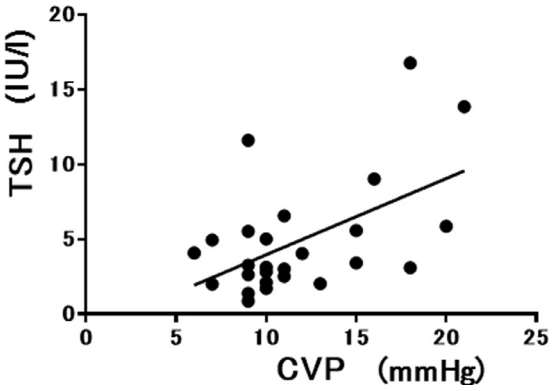

Figure 1. Relation between the TSH level and CVP.

Discussion

It has been increasingly recognized that end-organ damage, such as hepatic and renal dysfunction, protein-losing enteropathy, or plastic bronchitis, increases with time after the Fontan procedure due to its unique physiology of venous congestion.[3,10] This is the first study to demonstrate the thyroid gland as another potential organ that is damaged in patients with Fontan circulation. Although there were no patients with overt hypothyroidism, which is defined as decreased FT4 levels, 12 patients (33%) had SCH with elevated TSH levels. The prevalence is higher than the general Japanese population, which has been reported to be 3% to 7%.[11] Whether Fontan patients also showed that a higher prevalence of SCH compared with other forms of patients with congenital heart disease adjusted for age, age at intervention, and level of complexity would be clinically important and should be clarified in future studies. In this study, we also found a significant association between elevated CVP and increased TSH levels. Because TSH does not have a direct action on the cardiovascular function, but rather reflects decreased thyroid function, the result strongly suggests that elevated CVP of Fontan hemodynamics causes thyroid dysfunction through organ congestion. Significant association of increased blood volume, higher γGTP levels (liver congestion), and anemia (hemodilution) with low thyroid function (increased TSH levels) may also support the importance of venous congestion in thyroid dysfunction of patients with Fontan circulation.

The present study also provided important and novel findings that patients with SCH had lower FT3 levels than

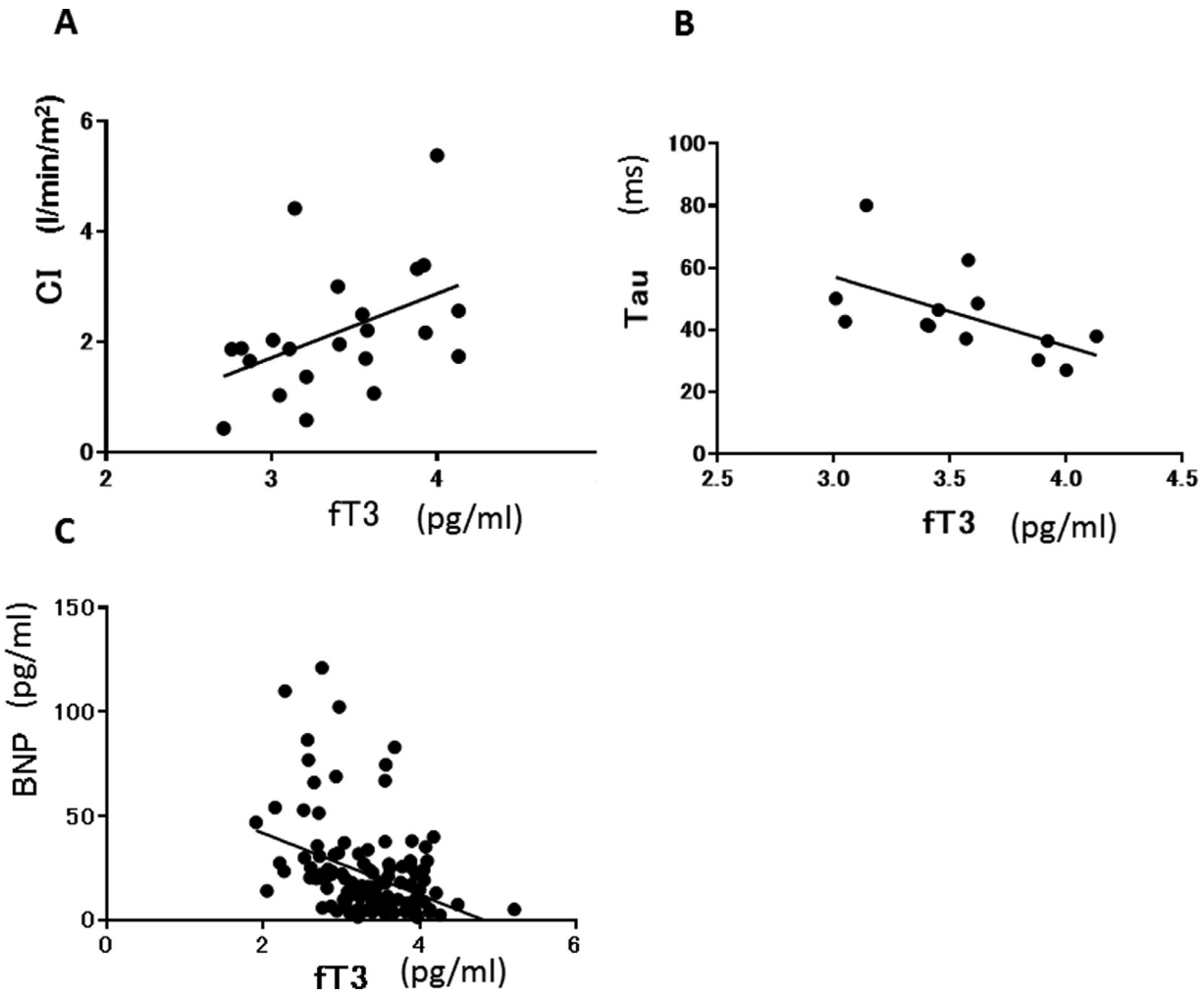

Figure 2. Relation of FT3 level with the (*A*), relaxation time constant (tau; *B*), and brain natriuretic hormone (BNP; *C*) level.

those with normal thyroid function, and that low FT3 levels were associated with decreased systolic and diastolic functions of patients with Fontan circulation. As shown in Figure 2, the FT3 level was significantly and negatively correlated with the relaxation time constant and positively correlated with CI. In addition, the FMD level, which is an indicator of endothelial function, was lower in patients with SCH than in patients with normal thyroid. Previous studies conducted in adults reported that SCH is associated with various adverse cardiovascular outcomes such as increased risk for atherosclerosis, heart failure, and coronary artery disease.[12–15] The underlying mechanisms are believed to be caused by the diverse actions of the thyroid hormone in the myocardium and vascular cells through specific triiodothyronine (T3) receptors.[7,16] For example, a low T3 level can induce myosin isoform switch from α- to β-myosin heavy chain[17] and downregulation of the sarcoplasmic reticulum calcium ATPase and phospholamban,[18,19] leading to impairment of myocardial contractility and relaxation. T3 also alters contractility through interactions with the β-adrenergic system.[20] In addition, T3 plays an important role in suppressing myocardial collagen accumulation through regulation of the matrix metalloproteinases and their inhibitors.[21,22] It also increases coronary and peripheral blood flow through the endothelial nitric oxide pathway, and low thyroid function promotes endothelial dysfunction due partly to elevated reactive oxygen species[23] and vascular smooth muscle cell apoptosis.[24–27]

The importance of thyroid function in the regulation of cardiovascular function is further supported by the evidence that thyroid hormone replacement therapy can help improve or reverse several abnormalities induced by low thyroid function or low T3, including systolic, diastolic, and endothelial dysfunction and myocardial fibrosis.[14,15,22,25–27] One study conducted in children with SCH examined the effect of L-thyroxine treatment on left ventricular functions.[28] Children with SCH had significant impairments in left ventricular diastolic and systolic functions as seen in the echocardiogram, which improved after 6 months when euthyroidism was achieved.[28] From these data, it is possible that substitution of the thyroid hormone in patients with SCH after the Fontan procedure may improve the ventricular function and resultant Fontan hemodynamics, which can break down a vicious cycle of thyroid dysfunction in the Fontan circulation, although we should be careful about the induction of such a therapy, particularly preventative replacement, because of potentially undesirable effects, such as a higher incidence of arrhythmias.

In conclusion, in addition to the well-known long-term complications after Fontan surgery, thyroid dysfunction with SCH should be considered as one of the post-Fontan complications associated with venous congestion. Decreased FT3 level among patients with SCH can cause ventricular contractile dysfunction, relaxation impairment, and endothelial dysfunction, possibly forming a vicious cycle of Fontan pathophysiology. Although cause-effect relations between thyroid dysfunction and Fontan hemodynamics remain to be determined by further studies, the present study suggests that thyroid function should be routinely monitored after Fontan surgery, and that thyroid hormone replacement therapy may be an effective treatment option to improve Fontan hemodynamics and outcome. This hypothesis requires further investigation with careful consideration for potential untoward effects.

1. Kim J, Kuwata S, Kurishima C, Iwamoto Y, Ishido H, Masutani S, Senzaki H. Importance of dynamic central venous pressure in Fontan circulation. *Heart Vessels* 2018;33:664–670.
2. Kurishima C, Saiki H, Masutani S, Senzaki H. Tailored therapy for aggressive dilatation of systemic veins and arteries may result in improved long-term Fontan circulation. *J Thorac Cardiovasc Surg* 2015;150:1367–1370.
3. Rychik J, Goldberg D, Rand E, Semeao E, Russo P, Dori Y, Dodds K. End-organ consequences of the Fontan operation: liver fibrosis, protein-losing enteropathy and plastic bronchitis. *Cardiol Young* 2013;23:831–840.
4. Saiki H, Kurishima C, Masutani S, Senzaki H. Cerebral circulation in patients with Fontan circulation: assessment by carotid arterial wave intensity and stiffness. *Ann Thorac Surg* 2014;97:1394–1399.
5. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med* 2001;344:501–509.
6. Klein I, Danzi S. Thyroid disease and the heart. *Circulation* 2007;116:1725–1735.
7. Gerdes AM. Restoration of thyroid hormone balance: a game changer in the treatment of heart failure? *Am J Physiol Heart Circ Physiol* 2015;308:H1–H10.
8. Masutani S, Kurishima C, Yana A, Kuwata S, Iwamoto Y, Saiki H, Ishido H, Senzaki H. Assessment of central venous physiology of Fontan circulation using peripheral venous pressure. *J Thorac Cardiovasc Surg* 2017;153:912–920.
9. Conway DS, Pearce LA, Chin BS, Hart RG, Lip GY. Plasma von Willebrand factor and soluble p-selectin as indices of endothelial damage and platelet activation in 1321 patients with nonvalvular atrial fibrillation: relationship to stroke risk factors. *Circulation* 2002;106:1962–1967.
10. Wilson TG, d'Udekem Y, Winlaw DS, Cordina RL, Celermajer DS, Wheaton GR, Bullock A, Gentles TL, Weintraub RG, Justo RN, Grigg LE, Radford DJ, Hardikar W, Cheung M, Cain TM, Rao P, Alexander SI, Ayer J, Verrall C, Du Plessis K, Chapman J, Rice K, Barry J, Zannino D, Iyengar AJ. Australian and New Zealand Fontan Registry. Hepatic and renal end-organ damage in the Fontan circulation: a report from the Australian and New Zealand Fontan Registry. *Int J Cardiol* 2018;273:100–107.
11. Isozaki O. Diagnostic approach: subclinical thyroid dysfunction (in Japanese). *J Jpn Soc Int Med* 2010;99:25–30.
12. Imaizumi M, Akahoshi M, Ichimaru S, Nakashima E, Hida A, Soda M, Usa T, Ashizawa K, Yokoyama N, Maeda R, Nagataki S, Eguchi K. Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. *J Clin Endocrinol Metab* 2004;89:3365–3370.
13. Kvetny J, Heldgaard PE, Bladbjerg EM, Gram J. Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. *Clin Endocrinol (Oxf)* 2004;61:232–238.
14. Chen S, Shauer A, Zwas DR, Lotan C, Keren A, Gotsman I. The effect of thyroid function on clinical outcome in patients with heart failure. *Eur J Heart Fail* 2014;16:217–226.
15. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med* 2000;132:270–278.
16. Martinez F. Thyroid hormones and heart failure. *Heart Fail Rev* 2016;21:361–364.
17. Bahouth SW, Cui X, Beauchamp MJ, Park EA. Thyroid hormone induces beta1-adrenergic receptor gene transcription through a direct repeat separated by five nucleotides. *J Mol Cell Cardiol* 1997;29:3223–3237.
18. Chang KC, Figueredo VM, Schreur JH, Kariya K, Weiner MW, Simpson PC, Camacho SA. Thyroid hormone improves function and Ca2+ handling in pressure overload hypertrophy. Association with increased sarcoplasmic reticulum Ca2+-ATPase and alpha-myosin heavy chain in rat hearts. *J Clin Invest* 1997;100:1742–1749.
19. Kiss E, Jakab G, Kranias EG, Edes I. Thyroid hormone-induced alterations in phospholamban protein expression. Regulatory effects on sarcoplasmic reticulum Ca2+ transport and myocardial relaxation. *Circ Res* 1994;75:245–251.

20. Williams LT, Lefkowitz RJ, Watanabe AM, Hathaway DR, Besch HR Jr.. Thyroid hormone regulation of beta-adrenergic receptor number. *J Biol Chem* 1977;252:2787–2789.
21. Wu Y, Peng J, Campbell KB, Labeit S, Granzier H. Hypothyroidism leads to increased collagen-based stiffness and re-expression of large cardiac titin isoforms with high compliance. *J Mol Cell Cardiol* 2007;42:186–195.
22. Ghose Roy S, Mishra S, Ghosh G, Bandyopadhyay A. Thyroid hormone induces myocardial matrix degradation by activating matrix metalloproteinase-1. *Matrix Biol* 2007;26:269–279.
23. Paolocci N, Biondi R, Bettini M, Lee CI, Berlowitz CO, Rossi R, Xia Y, Ambrosio G, L'Abbate A, Kass DA, Zweier JL. Oxygen radical-mediated reduction in basal and agonist-evoked no release in isolated rat heart. *J Mol Cell Cardiol* 2001;33:671–679.
24. Carrillo-Sepulveda MA, Ceravolo GS, Fortes ZB, Carvalho MH, Tostes RC, Laurindo FR, Webb RC, Barreto-Chaves ML. Thyroid hormone stimulates NO production via activation of the PI3K/Akt pathway in vascular myocytes. *Cardiovasc Res* 2010;85:560–570.
25. Hiroi Y, Kim HH, Ying H, Furuya F, Huang Z, Simoncini T, Noma K, Ueki K, Nguyen NH, Scanlan TS, Moskowitz MA, Cheng SY, Liao JK. Rapid nongenomic actions of thyroid hormone. *Proc Natl Acad Sci USA* 2006;103:14104–14109.
26. Wang P, Xu TY, Guan YF, Zhao Y, Li ZY, Lan XH, Wang X, Yang PY, Kang ZM, Vanhoutte PM, Miao CY. Vascular smooth muscle cell apoptosis is an early trigger for hypothyroid atherosclerosis. *Cardiovasc Res* 2014;102:448–459.
27. Lekakis J, Papamichael C, Alevizaki M, Piperingos G, Marafelia P, Mantzos J, Stamatelopoulos S, Koutras DA. Flow-mediated, endothelium-dependent vasodilation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (TSH) values. *Thyroid* 1997;7:411–414.
28. Catli G, Kir M, Anik A, Yilmaz N, Bober E, Abaci A. The effect of L-thyroxine treatment on left ventricular functions in children with subclinical hypothyroidism. *Arch Dis Child* 2015;100:130–137.