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Evaluation of epicardial fat thickness and carotid intima-media thickness in the patients with subclinical and overt hypothyroidism

Subklinik ve aşikar hipotiroidili hastalarda epikardiyal yağ kalınlığı ve karotisintima-media kalınlığının değerlendirilmesi

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Abstract

Introduction: The studies conducted have shown that epicardial fat thickness (EFT) and Carotid intima-media thickness (CIMT) are closely associated with cardiovascular diseases and that this may be an indicator for the prediction of early atherosclerosis. Inthisstudy, we have attempted toidentify EFT and CIMT in patients with hypothyroid is mand toreveal the relationship between them and thyroid hormones.

Methods: 82 patients diagnosed with primary hypothyroidism and 37 patients from healthy control group were included in the study. The subclinic hypothyroidism group (SH) was made up of 50 patients; the overt hypothyroidism group (OH) was composed of 32 patients. Cases' thyroid-stimulating hormone (TSH), FT3, FT4, thyroperoxidase antibodies (anti-tpo) and anti-tiroglobulinantibodies (anti-tg) were studied. Their EFT and CIMT values were measured. The statistical analysis was applied to EFT and CIMT.

Results: Compared with the CG, the thickness of epicardial fat tissue increased in OH and SH groups (p<0,001, p<0,001 respectively). In terms of EFT, there was no significant difference between OH and SH groups. Compared with the CG, the mean CIMT increased in OH and SH (p<0,001, p<0.001 respectively), but there was no significant difference between OH and SH in terms of CIMT. In addition, there was a positive correlation between EFT and CIMT (p<0.001).

Discussion and Conclusion: The measurement of EFT and CIMT can be used as a marker for the diagnosis of early atherosclerosis both in OH and in SH patients. Because the thickness of EFT and CIMT increased in patients with SH who are debated as to whether they should be treated, it leads us to think that these patients should be treated in order to reduce the risk of cardiovascular diseases in these patients.

Keywords: Epicardial fat thickness; carotid intima-media thickness; hypothyroidism.

Özet

Amaç: Aşikar olsun subklinik olsun hipotiroidininkardiyovasküler sistem üzerine birçok etkisi vardır. Epikardiyal yağ kalınlığı (EFT) ve Karotisintima-media kalınlığının (CIMT) kardiyovasküler hastalıklarla yakın ilişkisi yapılmış çalışmalarla ortaya konulmuş ve erken ateroklerozun öngörüsünde bir belirteç olabilecekleri belirtilmiştir. Bu çalışmada hipotiroidili hastalarda EFT ve CIMT değerlerini saptamayı ve bunların tiroid hormonları ile ilişkisini ortaya koymayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya 82 primerhipotiroidi tanılı hasta, 37 sağlıklı kontrol gubu (KG) olgusu dahil edildi. Subklinikhipotiroidi grubu (SH) 50; aşikarhipotiroidi grubu (AH) grubu 32 hastadan oluşuyordu. Olguların tiroid uyarıcı hormon (TSH), serbset t3 (FT3),serbest t4 (FT4), anti tiroidperoksidaz (anti-TPO), anti tiroglobülin (antı-TG) değerleri çalışıldı. EFT ve CIMT değerleri ölçüldü. EFT ve CIMT için korelasyon analizleri uygulandı. SPSS 18.0 bilgisayar programı ile çalışmanın istatistiksel değerlendirmesi yapıldı. P<0.05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Ortalama değerler EFT için SH, AH ve KG'da sırası ile 5.49±0.71 mm, 5.05±0.98 mm, 3.62±0.75 mm CIMT için SH, AH ve KG'da sırası ile 0.59±0.12mm, 0.58±0.12 mm, 0.43±0.8 mm bulundu. AH ve SH grupta KG'na göre EFT artmıştı (sırası ile p<0,001, p<0,001). AH ile SH grup arasında ise EFT yönüyle anlamlı farklılık yoktu. AH ve SH grupta KG'na göre CIMT artmıştı (sırası ile p<0,001, p<0.001). AH ile SH grup arasında ise CIMT yönüyle anlamlı farklılık yoktu. Ek olarak EFT ile CIMT arasında pozitif korelasyon vardı (p<0.001).

Sonuç: EFT ve CIMT ölçümü hem AH hem de SH hastalarda erken ateroskleroz için faydalı bir belirteç olarak kullanılabilir. Özellikle de tedavi edilip edilmemesi konusu tartışmalı olan SH hastalarda artmış EFT ve CIMT bulunması bu hastaların kardivasküler hastalık riskini azalmak için tedavi edilmesi gerektiğini göstermektedir.

Anahtar Sözcükler: Epikardiyal yağ kalınlığı; karotisintima-media kalınlığı; hipotiroidizm.

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Hypothyroidism is a syndrome characterized by tiredness, forgetfulness, indigestion, coarseness in voice, infertility, muscular pain and bradicardia (1). This clinical table is called primary hypothyroidism if it results from the inefficiency of thyroid gland, secondary hypothyroidism if it is caused by the inefficiency of TSH and tertiary hypothyroidism if it occurs as a result of the inefficiency of thyroid releasing hormone. The most common reason for primary hypothyroidism is hashimoto thyroiditis and is divided into overt and subclinical hypothyroidism based on the serum TSH level (2, 3). High TSH level is classified as overt hypothyroidism when free T3 (FT3) and/or free T4 (FT4) levels are low; high TSH and the absence of clinical indicators of overt hypothyroidism when FT3 and FT4 are normal is called subclinical hypothyroid. Subclinic hypothyroidism is a case clinicians frequently encounter in daily practice. The main question is whether these patients should be treated or followed without treatment. It is noted that EFT is an important risk factor for coronary arterial disease (CAD) and that it is a marker of visceral fat tissue around myocardium correlated with central obesity (4). What kind of relationship EFT and CIMT have with CAD is a topic heatedly debated today. In the studies conducted, it was found that there is a significant relationship between CIMT and coronary vascular disease (CVD), and it is thus stated that CIMT could be used in predicting the risk of CVD (5). Hypothyroidism, particularly the relationship of SH with EFT and CIMT, has become the subject of research in recent years, but there are a limited number of studies in this regard. In our study, we have tried to throw light on the relationship between subclinic hypothyroidism and CVD, which is not still clear, by measuring EFT and CIMT in patients with hypothyroidism.

Materials and Method

The patients diagnosed with hypothyroidism when they applied to the Medical Faculty of Dicle University were included in this study. We included 82 patients diagnosed with hypothyroidism and 37 healthy patients as control group in the study. The patients diagnosed with hypothyroidism were separated into two subgroups, OH and SH, depending on their levels of TSH and FT4 levels. The patients with increased TSH (>4, 20 mIU/mL), decreased FT4 (<12 mIU/mL) and positive (>35 mIU/mL) antı-tpo were designated as OH group, whereas the patients with increased TSH, normal FT4 and positive anti-tpo were designated as in the SH group. There were 8 male and 42 female patients in the SH group, 4 male and 28 female patients in the OH groups. Those with such conditions as a known heart disease, the metabolic syndrome, diabetes mellitus, obesity (BMI>30) and hypertension (TA>140/90) were not included in the study. The systolic blood pressures (SBP) and diastolic blood pressures (DBP) of the patients were measured with mercury sphygmomanometer while they were sitting in a silent environment and recorded. EFT of the patients was measured with transthoracic echocardiography and their CIMT was measured with a doppler ultrasound device. Therightandleftside CIMT wasmeasuredandmeanvalueswererecorded. The control group was made up of healthy volunteers with no known chronic disease. Written consent was obtained from all the volunteers. An application was filed to the medical research ethical board of Dicle University. After the approval was confirmed, the study was started (project no: 223, confirmation date: April 15, 2015).

Hormone and biochemical measurements

TSH, FT3, FT4 anti-tpo and anti-tg antibody titers, insulin levels, LDL-cholesterol (LDL-c), HDL- cholesterol (HDL-c), triglyceride (TG), total- cholesterol (T- chol) and VLDL-c values of the cases were studied. Their levels of TSH, FT4, FT3, anti-tg and anti-tpo were measured with the method of Electrochemiluminescence Immunoassay (ECLIA). The ranges of 0.270-4.20 mIU/mL for TSH, 12-22 pmol/L for FT4 and 0-35 IU/mL for anti-tpo were accepted as normal values for euthyroidism.

Epicardial fat thickness and carotid intima-media thickness measurement

EFT in all cases was evaluated through an HP HD 211 (Philips Holland) Electrocardiographic device and 2,5 MHz electrocardiography probe. EFT was measured in "mm" by an experienced cardiologist who had no knowledge of the clinical and demographic traits of the patients through a 2-D echocardiography device from parasternal long axis and parasternal short axis images over the right ventricular free wall. CIMT was measured through an ultrasonography device (AlokaProsound SSD 5000 machine; Japan) using a probe of 7,5 mHz linear probe, from the right and left main carotid artery in a longitudinal position 10 mm proximal to bifurcation. The mean values of the measurements of the both sides were recorded in "mm".

Statistical analysis

The statistical evaluation of the study was conducted through SPSS 18.0 (statistical package for social sciences). The value of $P<0.05$ was considered statistically significant. The results were given as mean±SD and percent (%). In order to compare all the three groups, one-way Anova test was used. The independent t-test was employed for the comparison of two groups, and the student t-test was used for the comparisons between the groups and variables. The Pearson correlation variables were used for the correlation analysis between parameters. The regression analysis was carried out through such variables as EFT and CIMT dependent variables, age, BMI, SBP, DBP, TSH, FT4, FT3, LDL-c, HDL-c, TG, T-chol and VLDL-c.

Results

50 SH patients, 32 OH patients and 37 CG patients were included in the study. The average ages of the patients were measured to be 35,3±9,5 and 37,4±9,6 for SH and OH groups respectively. The comparison of the findings in all the three groups is given in brief in Table 1. Gender, age, BMI, FPG, SBP, DBP, LDL-c, HDL-c, T-chol and TG levels did not differ significantly among the three groups. Levels of serum TSH, FT4, FT3, anti- tpo, anti-tg and Homa-IR differed significantly among

Table 1. Clinic laboratory and echocardiographic data for all study cases

Parameters	SH	OH	CG	P
Gender (M/F)	8/42	4/28	6/31	NS
Age (year)	35.3± 9.5	37.4±9.6	35.6±1.9	NS
BMI (kg/m^2)	25.2± 3.8	26.2±3.9	31.4±44.9	NS
SBP (mm/Hg)	119.4±12.8	124.8±13.1	120.9±13.8	NS
DBP (mm/Hg)	74.0±8.9	78.20±9.5	74.7±7.3	NS
TSH (mIU/mL)	**7.9±3.6**	**18.8±16.2**	**1.6±0.8**	**<0.001**
FT3 (pmol/L)	**4.8±0.8**	**4.3±1.3**	**5.2±0.6**	**0.001**
FT4 (pmol/L)	**14.7±1.8**	**9.7±2.4**	**16.4±2.1**	**<0.001**
Anti-TPO (IU/mL)	**207.3±227.1**	**216.5±210.8**	**16.4±18.5**	**<0.001**
Anti-TG (IU/mL)	**617.3±1164.6**	**299.0±667.7**	**43.1±74.8**	**0.008**
FPG (mg/dl)	95.3±7.3	95.9±7.6	92.7±7.7	NS
HOMA IR	**2.4±1.7**	**3.7±3.6**	**2.3±1.0**	**0.018**
LDL-col (mg/dl)	108.1±38.1	117.7±35.0	103.0±26.5	NS
HDL-col (mg/dl)	50.3±11.8	49.4±11.1	46.6±11.9	NS
VLDL-col (mg/dl)	**21.6±10.2**	**45.5±60.6**	**20.4±10.1**	**0.002**
T-chol (mg/d)	181.7±37.4	178.5±75.9	169.0±34.8	NS
TG (mg/dl)	104.7±52.7	106.1±111.1	102.6±57.5	NS
EFT (mm)	**5.49±0.71**	**5.05±0.98**	**3.62±0.75**	**<0.001**
CIMT (mm)	**0.59±0.12**	**0.58±0.12**	**0.43±0.8**	**<0.001**

NS: Not significant; CG: Control group; SH: Subclinic hypothyroidism group; OH: Overt hypothyroidism group; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressur.

Table 2. Comparison between whole study groups for EFT and CIMT

	SH CG	CG OH	OH SH
EFT	**<0.001**	**<0.001**	NS
CIMT	**<0.001**	**<0.001**	NS

NS: Not significant; CG: Control group; SH: Subclinic hypothyroidism group; OH: Over thypothyroidism group.

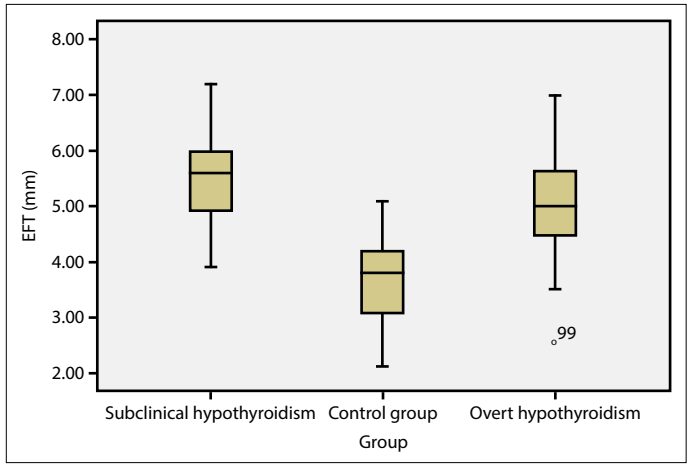

Figure 1. Box plot presentation of epicardial fat thickness in study participants.

the three groups. When the patient groups were evaluated separately, the values of TSH, anti-tpo, anti-tg were detected to be significantly high in SH group compared with the CG (p<0.001). However, there was no significant difference in terms of age, FT3, FT4 and Homa-IR values between the two groups (Table 1).

TSH and anti-tpo values were significantly high in OH group compared with the CG (p<0.001). There was a significant difference between the two groups in the values of Homa-IR, anti-tg, VLDL-c, FT3 and FT4. There was no significant difference between the SH group and the CG in the levels of Homa-IR, FT3 and FT4. Compared with the SH group TSH, homa-IR and VLDL-c were significantly high in OH group; yet, FT3 and FT4 were significantly low. EFT and CIMT values in the SH were detected to be significantly higher than those in the CG (p<0.001, p<0.001 respectively). Similarly, EFT and CIMT values in the OH group had increased significantly compared with the values in the CG (p<0.001, p<0.001). OH and SH groups were compared with each other. There was no significant difference between the two groups either in EFT and CIMT values. The relationship concerning EFT and CIMT between the groups are shown in Table 2, Figures 1 and 2.

The regression analysis between EFT and CIMT and all the patients in the study is shown in Table 3 and Table 4 respectively.

As seen in the tables, EFT had a significantly positive correlation with age, TSH, anti-tpo, anti-tg and CIMT, yet it had a negative correlation with FT3 and FT4. CIMT had a signifi-

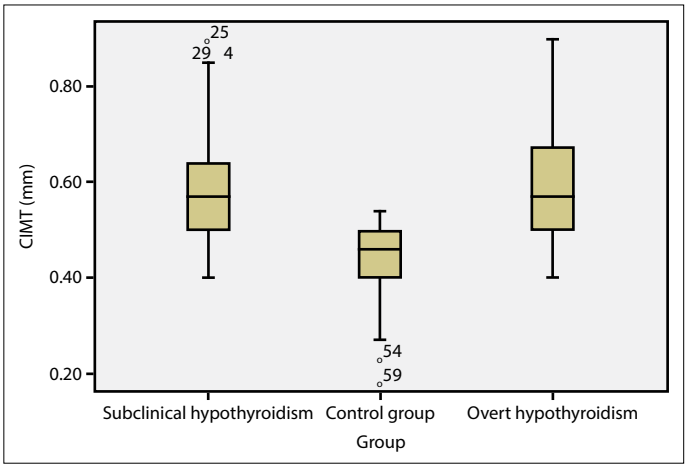

Figure 2. Box plot presentation of carotid intima-media thickness in study participants.

Table 3. Pearson correlation analysis between epicardial fat thickness and other parameters in the whole study group

	r	p		r	p
Age	**0.210**	**0.022**	Anti-TG	0.317	**<0.001**
BMI	0.130	NS	HOMA IR	-0.024	NS
SBP	0.137	NS	LDL-col	0.124	NS
DBP	0.173	NS	HDL	0.093	NS
TSH	**0.190**	**0.038**	VLDL	0.046	NS
FT3	**-0.242**	**0.008**	T-col	0.086	NS
FT4	**-0.193**	**0.035**	TG	0.026	NS
Anti-TPO	**0.440**	**<0.001**	CIMT	**0.695**	**<0.001**

BMI: Body mass index; NS: Not significant;.

Table 4. Pearson correlation analysis between carotid intima-media thickness and other parameters in the whole study group

	r	p		r	p
Age	**0.244**	**0.008**	Anti-TG	**0.320**	**<0.001**
BMI	-0.002	NS	HOMA IR	0.013	NS
SBP	0.132	NS	LDL-col	0.137	NS
DBP	0.159	NS	HDL	0.117	NS
TSH	**0.283**	**0.002**	VLDL	0.157	NS
FT3	**-0.279**	**0.002**	T-col	0.030	NS
FT4	**-0.193**	**0.036**	TG	0.035	NS
Anti-TPO	**0.474**	**<0.001**	EFT	**0.695**	**<0.001**

BMI: Body mass index; NS: Not significant;.

cantly positive correlation with age, TSH, anti-tpo, anti-tg, EFT and a negative correlation with FT3 and FT4. There was a positive correlation between EFT and CIMT (p<0.001). The relationship of TSH, FT3 and FT4 hormone levels with EFT and CIMT was evaluated. According to the Pearson correlation analysis, a positive relationship was seen between the level of TSH and EFT and CIMT. When the level of FT3 was compared with EFT and CIMT, there was a positive correlation between them. When the level of FT4 was compared with EFT and CIMT, a negative correlation similar the one between FT3 and EFT and CIMT was present between them. While the level of FT4 decreased, a significant increase was observed in the levels of EFT and CIMT. When a comparison was made between the values of EFT and CIMT and the levels of anti-tpo and anti-tg in the patients, both EFT and CIMT were positively correlated with both anti-tpo and anti-tg values (p<0.001). When the relationship of EFT and CIMT values with age, BMI, SBP, DBP, FPG, Homa-IR, LDL-c, HDL-c, VLDL-c, T-chol and TG was evaluated, it was seen that there was a significant increase between each of them and age but that there was no significant increase between the other variables and each of them.

Discussion

Atherosclerosis, commonly seen today, is the most frequent cause of mortality and morbidity. CVD, developing on the basis of atherosclerosis, now comes on top among the causes of death (6). The studies carried out in recent years have highlighted EFT and CIMT too among the risk factors of atherosclerosis. It is recognized that inflammation in the epicardial fat tissue might play a role in coronary atherosclerosis through its effects on vasocrine and paracrine (7, 8). It is stated in a number of studies that hypothyroidism induces CAD and that CAD increases in patients with hypothyroid, which is explained to be correlated with an increase in the levels of T-chol, LDL-c, lipoprotein-a and homosistein, which have an aterogenic effect (1). Increased LDL-c, hypercoagulability, obesity, systolic and diastolic hypertension are the mechanisms blamed for the development of atherosclerosis plaque in the patients with hypothyroidism (9). The relationship between SH and CAD has been the subject of a lot of research, and according to the results of a meta-analysis covering 10 studies, there is at moderate relationship between SH and increased CAD and mortality (10). It is also asserted that the major mechanism behind the development of atherosclerosis in SH is a disorder in the lipid profile and endothelial dysfunction resulting from it (11). Because EFT is not affected by subcutaneous fat tissue, it is accepted as a good marker in determining the risks of both visceral fattening and the resulting CVD (12). Joeng et al. (13) found a positive correlation between severe CAD and EFT in their study. In another study on SH and OH patients, Asık et al. (14) identified that EFT increased both in SH and CAD patients. On the other hand, in a recent published study, Korkmaz et al. (15) found that EFT increased not in all SH patients but just in patients with TSH>10 mIU/L. Santos et al. (16) found that there was not a significant increase in EFT in SH patients with TSH <10 mIU/L, compared with the control group and maintained that using EFT wouldn't be useful as an early marker for atherosclerosis. However, in our study, EFT increased significantly both in OH and SH groups compared with the CG.

We didn't classify SH patients on the basis of TSH 10 mIU/L, but there was a linear correlation between TSH and EFT level. Based on these findings, it could be stated that it may not be

true to give a threshold value for an increase in EFT in SH and that any increase in the level of TSH may be correlated with an increase in EFT. It is a well-known fact that the expression of TSH receptor increases on the surface of adiposits during the process in which adiposits differentiate and mature (17). Therefore, it may be thought that, in hypothyroid, an increased TSH level could lead to an increase in visceral adipose tissue, and this, in turn, may pose a risk for atherosclerosis and CVD. When OH and SH patients were compared with each other in terms of EFT, no significant difference was observed. The rate of increase was similar in both groups. This suggests that both OH and SH patients are at nearly the same risk for atherosclerosis. The studies conducted have concluded that CIMT has increased in OH, but the relationship between SH and CIMT has continued to be a controversial issue. Some studies found that CIMT had increased in SH (18), whereas others failed to find a relationship between the two (14, 15). In their study (18), Nagasaki T. et al. detected an increase in CIMT in OH and SCH patients. On the other hand, Santos et al.(16) detected that CIMT increased in OH but that it didn't increase in SH. In our study, we found that CIMT increased in the patients with OH compared with the CG. We also detected CIMT to be high in SH group about which differing views are present, compared with the control group. When we compared OH and SH groups with each other, we failed to find a significant difference in terms of CIMT. There are studies stating that a chronic inflammation in hypothyroidism leads to an increase in CIMT (19, 20). Because we detected high antibody titers in the patients in our study, our study supports the view that a chronic inflammation leads to an increase in CIMT. That fact that EFT and CIMT were high in SH and OH groups compared with CG but similar to each other indicates that SH should also be evaluated, like OH, in terms of the risk for atherosclerosis and CVD. A reason that EFT and CIMT were detected to be high in our patients with hypothyroidism could also be dislipidemia (increased T-chol and LDL-c levels), as our patients both with SH and OH had increased LDL-c, TG, T-chol and VLDL-c levels, compared with the CG. Our study also supports the view that EFT and CIMT could be an early marker for coronary atherosclerosis in SH and OH patients. Recent studies have maintained that CIMT increases in the patients with hypothyroidism even if thyroid functions are normal and that it could be related to an autoimmune thyroid disease in the background (21). In their study, Asık et al. (14) found that the level of anti-tpo in SH and OH groups was significantly higher than in the control group but didn't identify a positive correlation between the level of anti-tpo and EFT. In our study, however, we identified a positive correlation between TSH and the levels of EFT and CIMT. When the patients were grouped as SH and OH and their EFT and CIMT were examined, they were found to be higher than in the control group (Figs. 1 and 2).

In both of the groups, anti-tpo and anti-tg levels were significantly higher than in the control group, and a positive correlation was detected between antibody titers and EFT and CIMT, unlike the cases in the aforementioned studies. Because an increase in the on the body titers reflects and inflammatory situation, we are of the opinion that the inflammatory process might have a role in the increase in EFT and CIMT in hypothyroid. Because the severity of hypothyroidism disease is correlated with high TSH level, low FT4 level and high antibody titers, the risk of atherosclerosis and CVD would increase in SH and OH with serious or untreated hypothyroid. Markers that foretell this risk may be the increased EFT and CIMT in patients with hypothyroidism as well. When the values of EFT and CIMT were compared with each other, a positive correlation was seen between them. This positive relationship, which is similar to the one we identified, is revealed in a number of studies (14, 22, and 23). In a sense, EFT turns out to be an indirect marker of CIMT. Because the measurement of EFT is a more challenging process than the measurement of CIMT, it could be considered viable to use CIMT instead of EFT in predicting the risk of atherosclerosis and CVD in patients with hypothyroid.

In conclusion, EFT and CIMT increased both in OH and SH patients compared with the normal population; therefore, measuring EFT and CIMT may be useful in predicting and preventing the risk of early atherosclerosis. Furthermore, the fact that EFT and CIMT increased in SH as in OH requires considering SH, like OH, for the risk of atherosclerosis. Particularly the patients about whom differing views exist as to whether they should be treated or not should be treated so that atherosclerosis risk factors may be reduced, even if they are not symptomatic.

Conflict of interest: There are no relevant conflicts of interest to disclose.

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