Low serum free triiodothyronine levels are associated with the presence and severity of coronary artery disease in the euthyroid patients: an observational study

Ötiroid hastalarda düşük serum FT3 düzeyleri koroner arter hastalığının varlığı ve şiddeti ile ilişkilidir: Gözlemsel bir çalışma

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ABSTRACT

Objective: The aim of this study is to investigate the relationship between serum thyroid hormone levels that are within the normal range and the presence and severity of coronary artery disease (CAD) in patients referred for coronary angiography.

Methods: In this observational study, we enrolled 119 consecutive patients (77 men, mean age 60.7±13.8 years) who underwent coronary angiography. Blood samples were tested for thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) concentrations. Additionally, risk factors, clinical characteristics and angiographic results were obtained. The patients were separated into two groups according to the Gensini score as those with mild or severe atherosclerosis. Statistical analysis was performed using the Chi-square, Mann-Whitney U, correlation and logistic regression tests, and ROC analysis.

Results: FT3 levels were significantly lower in subjects with CAD (4.0±0.7 vs. 4.6±0.6 pmol/L; p<0.001). Moreover, lower FT3 levels were found in patients with severe atherosclerosis (3.9±0.7 vs. 4.5±0.6 pmol/L; p<0.001). Logistic regression analysis demonstrated that the lower FT3 levels were associated with the presence (OR =0.266, 95% CI: 0.097-0.731, p=0.01) and severity (OR=0.238, 95% CI:0.083-0.685, p=0.008) of CAD. In the ROC analysis, a level of FT3 ≤4.2 pmol/L was found to predict the presence of CAD with 69% sensitivity and 71% specificity (AUC:0.744, 95% CI:0.653-0.834, p<0.001); and the severity of CAD with 75% sensitivity and 67% specificity (AUC:0.733, 95% CI:0.642-0.824, p<0.001).

Conclusions: FT3 levels within the normal range were inversely correlated with the presence and severity of CAD. Moreover, lower FT3 concentrations were correlated with the Gensini score and independently predicted the presence and severity of CAD. Thus, the FT3 levels may be used as the indicator of increased risk for CAD. *(Anadolu Kardiyol Derg 2012; 12: 591-6)*

Key words: Coronary artery disease, Gensini score, thyroid hormone levels, regression analysis, sensitivity, specificity

ÖZET

Amaç: Çalışmamızın amacı, koroner anjiyografi için kaynak gösterilen hastalarda normal sınırlardaki tiroid hormon düzeylerinin koroner arter hastalığının (KAH) varlığı ve şiddeti ile ilişkisini araştırmaktır.

Yöntem: Bu gözlemsel çalışmaya koroner anjiyografi yapılan ardışık 119 hasta (77 erkek, ortalama yaş 60.7±13.8 yıl) alındı. Serum serbest triiyodotironin (FT3), serbest tiroksin (FT4) ve tiroid uyarıcı hormon (TSH) düzeyleri alınan kan örneklerinde test edildi. Hastaların konvansiyonel risk faktörleri, klinik karakteristikleri ve anjiyografi sonuçları değerlendirildi. Hastalar Gensini skoruna göre hafif ve şiddetli ateroskleroz olarak iki ayrı gruba ayrıldı. İstatistiksel analiz olarak Ki-kare, Mann-Whitney U testleri ve korelasyon, lojistik regresyon ve ROC analizleri kullanıldı.

Bulgular: Serum FT3 düzeyleri KAH'ı olan kişilerde olmayanlara oranla önemli ölçüde düşük bulundu (4.0±0.7 karşı 4.6±0.6 pmol/L; p<0.001). Ayrıca, şiddetli aterosklerozu olan hastalarda FT3 düzeyleri önemli ölçüde düşüktü (3.9±0.7 karşı 4.5±0.6 pmol/L; p<0.001). Lojistik regresyon analizinde düşük FT3 düzeylerinin KAH'ın varlığı (OR:0.266, 95% GA:0.097-0.731, p=0.01) ve şiddeti (OR:0.238, 95% GA:0.083-0.685, p=0.008) ile ilişkili olduğu gösterildi. ROC analizinde FT3 seviyesinin ≤4.2 pmol/L olması KAH varlığını %69 duyarlılık ve %71 özgüllük ile (EAA:0.744, 95% GA:0.653-0.834,

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p<0.001), KAH şiddetini ise %75 duyarlılık ve %71 özgüllük ile (EAA:0.744, 95% GA:0.653-0.834, p<0.001) tespit edebiliyordu.
Sonuç: Normal sınırlardaki FT3 düzeyleri koroner anjiyografi için kaynak gösterilen hastalarda KAH'ın varlığı ve şiddeti ile ters ilişkilidir. Ayrıca düşük FT3 düzeyleri Gensini skoru ile korelasyon gösterip KAH'ın varlığı ve şiddetinin bağımsız bir prediktörüdür. Düşük FT3 düzeyleri KAH riskini belirlemekte kullanılabilir. *(Anadolu Kardiyol Derg 2012; 12: 591-6)*
Anahtar kelimeler: Gensini skoru, koroner arter hastalığı, tiroid hormon düzeyleri, regresyon analizi, duyarlılık, özgüllük

Introduction

Thyroid hormones have numerous effects on the heart and the cardiovascular system (1, 2). Although hyperthyroid state is generally associated with increased cardiovascular morbidity and mortality (3, 4), a high prevalence of coronary artery disease (CAD) in overt hypothyroidism has also been widely reported (5, 6). The relationship between thyroid hormone excess and CAD remains unclear (7-9). Several studies have shown an association between the thyroid function and atherosclerosis. However, most of these studies were conducted on patients with thyroid dysfunction. There are only a limited number of studies that have focused on the effect of the thyroid hormone levels within the normal ranges on CAD (10, 11). Auer et al. (10) have studied the severity of CAD in euthyroid patients, but without using the Gensini scores. Yun et al. (11) have reported that the thyroid-stimulating hormone (TSH) is not an independent predictor for CAD in patients with normal thyroid function. However, free triiodothyronine (FT3), which is an active metabolite of thyroid hormones, was not evaluated in this study. Therefore, we have examined the relationship between the serum thyroid hormone levels [TSH, FT3 and free thyroxin (FT4)] within the normal ranges and the presence and severity of CAD by using the Gensini scores in the euthyroid patients.

Methods

Study design

The present study was designed as a cross-sectional, observational study. Signed consent forms were obtained from all participants and the approval of the institutional review board was obtained prior to the initiation of the study.

Study population

A total of 119 consecutive euthyroid stable angina pectoris patients (77 men, mean age 60.7±13.8 years) who underwent coronary angiography in the Department of Cardiology, from April to October, 2011 were enrolled in the study. The patient histories were recorded and each patient was given a complete physical examination. Patients with a history of thyroid problems, acute coronary syndrome, acute infectious disease, chronic kidney and hepatic diseases or malignant tumors were excluded from the study. None of the patients had previously received any anti-thyroid treatment before the enrollment in this study. In addition, those who were prescribed amiodarone, which is an agent with a potential influence on thyroid functions, were also excluded. The presence of cardiovascular risk factors in the patient group was studied.

Coronary angiography

Coronary angiography was performed through the femoral artery access using the Judkins technique and the angiograms were visually evaluated by two interventional cardiologists who were blinded to the study plan and to each other. A thorough review of each coronary angiographic index established the lesion location and the percentage of stenosis among all the coronary lesions. Coronary artery disease was defined as >50% stenosis in the luminal diameter in at least one major epicardial coronary artery (12).

The Gensini scoring system was utilized to describe the severity of the CAD (13). This method grades the narrowing in the lumen of the coronary arteries as 1 for 1-25% stenosis, 2 for 26-50%, 4 for 51-75%, 8 for 76-90%, 16 for 91-99%, and 32 for total occlusion. The score is then multiplied by a factor representing the importance of the lesion's location in the coronary artery system. For the location scores, 5 points are given for left main lesion; 2.5 for proximal left anterior descending (LAD) or left circumflex (LCX) artery; 1.5 for the mid-segment LAD and LCX; 1 for the distal segment of LAD and LCX, first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery, and intermediate artery; and 0.5 for the second diagonal and second obtuse marginal branches.

According to presence of CAD, the patients were divided into two groups as those with CAD (n=84) and those with absent or minimal atherosclerotic involvement (n=35). Additionally, they were separated into two groups according to Gensini scoring: those with mild (n=51; Gensini score, 1-20; mild atherosclerosis) and severe atherosclerosis (n=68; Gensini score, >20; severe atherosclerosis) (14).

Laboratory tests

On admission, blood sampling was performed before the coronary angiography in order to measure the levels of glucose, creatinine, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol assayed using the routine laboratory techniques. Serum TSH, FT3 and FT4 levels were measured by the chemiluminescence method using the Cobas e601 analyzer (Roche, Mannheim, Germany). The inter-assay coefficients of variation were below 3.0%. The reference ranges in use in our laboratory are as follows: TSH=0.270 to 4.2 mU/L; FT3=3.9 to 6.7 pmol/L; and FT4=12 to 22 pmol/L.

Statistical analysis

The statistical analysis was performed using the SPSS for Windows version 15.0 (SPSS Inc Chicago, IL, USA). All variables

were tested in terms of the normal distribution using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean±standard deviation and categorical variables are expressed in number and percentage. Student's t-test or the Mann-Whitney U test was used for the comparison of continuous variables and the Chi-square test was used for comparison of the categorical changes. The relationships between the variables were examined with the help of Spearman's correlation coefficients. The cut-off value of FT3 for predicting the presence and severity of CAD with corresponding sensitivity and specificity was estimated through the receiver operating characteristic (ROC) curve analysis. A binary logistic regression analysis was performed to evaluate the independent predictive values of the potential variables of FT3, gender, total cholesterol, HDL, creatinine, glucose and EF for the presence and severity of CAD.

Results

Clinical characteristics of the patients

Baseline demographic, clinical and biochemical characteristics of the study groups are outlined in Table 1. The CAD group was observed to have a higher mean age and lower ejection fraction compared to the non-CAD group. Additionally, the ratio of male gender was significantly higher in the CAD group in comparison to the non-CAD group. Conversely, the total cholesterol, HDL and triglyceride concentrations were significantly higher in the non-CAD group compared to the CAD group. Serum glucose and creatinine concentrations were significantly higher in the CAD group than the non-CAD group. The LDL levels were observed to be similar in both groups.

Thyroid functions of the patients

While the FT3 levels were significantly lower in the subjects with CAD (4.6±0.6 vs. 4.0±0.7 pmol/L, p<0.001) (Fig. 1a), the FT4 and TSH levels were similar in both groups. In addition, the FT3 levels were lower in patients with severe atherosclerosis compared to those with mild atherosclerosis (3.9±0.7 vs. 4.5±0.6 pmol/L, p<0.001) (Fig. 1b). However, the FT4 and TSH values were similar (15.1±2.5 vs. 14.9±2.1 pmol/L, p=0.727; 1.2±0.9 vs. 1.3±0.8 pmol/L, p=0.415, respectively).

Clinical predictors of CAD

There was a significant correlation between the FT3 levels and the Gensini score (r=-0.398, p<0.001), age (r=-0.508, p<0.001), ejection fraction (r=0.306, p=0.01) and serum fasting glucose values (r=-0.195, p=0.034). After the adjustment for the conventional risk factors through the multivariate logistic regression analysis, the FT3 levels remained as a significant predictor of CAD (OR: 0.266, 95% CI: 0.097-0.731, p=0.01) (Table 2). On the other hand, the TSH and FT4 did not emerge as significant predictors. In addition, FT3 remained as a significant predictor of the severity of CAD (OR: 0.238, 95% CI: 0.083-0.685, p=0.008) (Table 3).

By the ROC analysis, a level of FT3 ≤ 4.2 predicted the presence of CAD with a 69% sensitivity and 71% specificity [(area under curve (AUC): 0.744, 95% CI: 0.653-0.834, p<0.001)], while it predicted the severity of CAD with 75% sensitivity and 67% specificity (AUC: 0.733, 95% CI: 0.642-0.824, p<0.001) in euthyroid patients (Fig. 2).

Table 1. Baseline characteristics of patients in CAD and non-CAD groups

Variables	Non-CAD (n=35)	CAD (n=84)	*p
Age, years	56.0±14.4 57 (24-83)	62.7±13.1 63 (39-88)	0.015
Male, n, %	16 (46)	61 (73)	0.005
Ejection fraction, %	55.2±13.6	47.4±11.1	0.002
Coronary risk factors			
Family history of CAD, n (%)	5 (14)	11 (13)	0.862
Smoking, n (%)	9 (26)	31 (37)	0.239
Arterial hypertension, n (%)	11 (31)	32 (38)	0.490
Diabetes mellitus, n (%)	5 (14)	18 (21)	0.369
Laboratory analyses			
Total cholesterol, mg/dL	181.0±42.3	163.9±36.2	0.027
LDL, mg/dL	110.0±33.4	100.6±28.7	0.126
HDL, mg/dL	41.1±9.1	35.3±9.0	0.002
Triglyceride, mg/dL	158.3±81.0	146.6±92.3	0.515
Creatinine, mg/dL	0.8±0.14.49	1.0±0.3	0.003
Glucose, mg/dL	116.1±43.1	142.2±61.7	0.025
FT3, pmol/L	4.6±0.6 4.5 (3.8-6.3)	4.0±0.7 4.0 (3.7-5.3)	<0.001
FT4, pmol/L	15.1±2.1 14.4 (12.2-20.0)	15.0±2.4 15.1 (12.1-21.9)	0.688
TSH, uil/mL	1.2±0.9 1.1 (0.3-4.1)	1.2±0.9 1.1 (0.3-4.1)	0.850

Data are presented as mean±SD, median (min-max) values and number (percentage)
*Student t-test, Mann-Whitney U test, Chi-square test
CAD - coronary artery disease, FT3 - free triiodothyronine, FT4 - free thyroxine, HDL - high density lipoprotein, LDL - low density lipoprotein, TSH - thyroid stimulating hormone

Table 2. Predictors of presence of CAD by logistic regression analysis

Variables	Odds ratio (%95 CI)	p
FT3, pmol/L	0.266 (0.097-0.731)	0.010
Age, year	1.041 (0.993-1.092)	0.096
Male, n, %	0.264 (0.071-0.977)	0.046
Total cholesterol, mg/dL	1.003 (0.989-1.018)	0.654
HDL, mg/dL	0.916 (0.855-0.981)	0.012
Creatinine, mg/dL	0.934 (0.403-2.162)	0.163
Glucose, mg/dL	1.002 (0.989-1.015)	0.076
Ejection fraction, %	0.977 (0.928-1.028)	0.363

FT3 - free triiodothyronine, HDL - high density lipoprotein

Discussion

The present study demonstrated that lower FT3 levels are an independent predictor of the presence and severity of CAD in

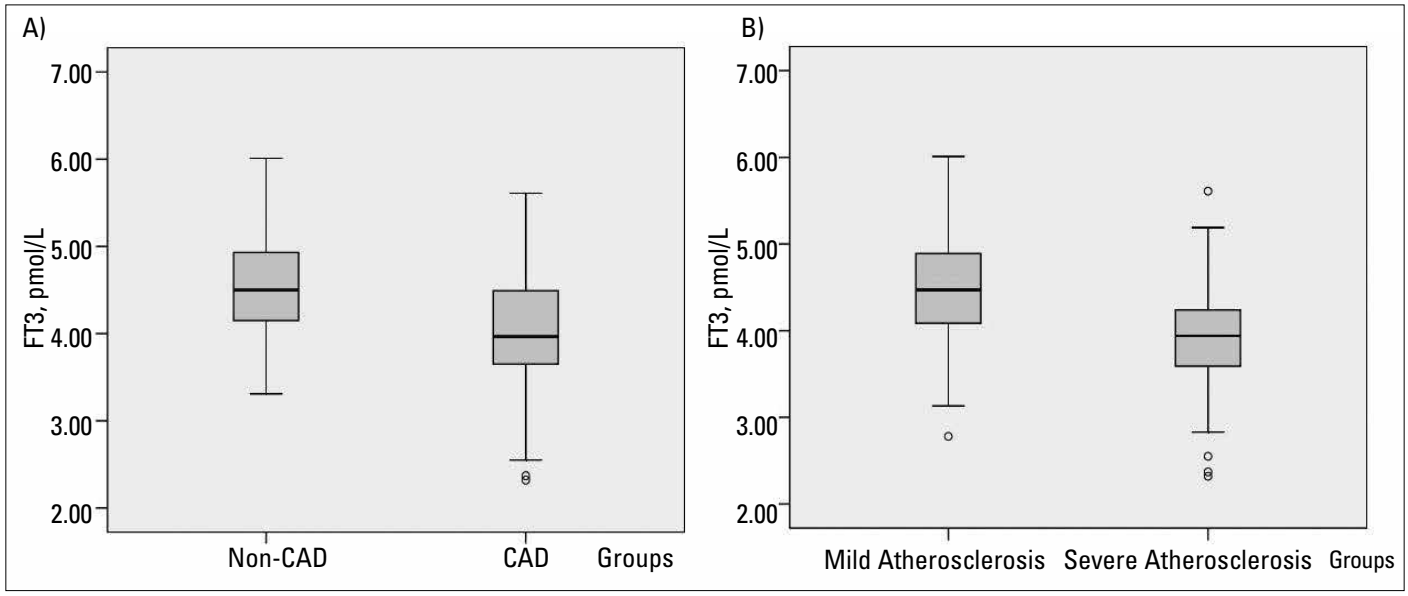

Figure 1. Box plot of FT3 levels in patients with and without CAD (a), and patients with mild and severe atherosclerosis (b)
CAD - coronary artery disease, FT3 - free triiodothyronine

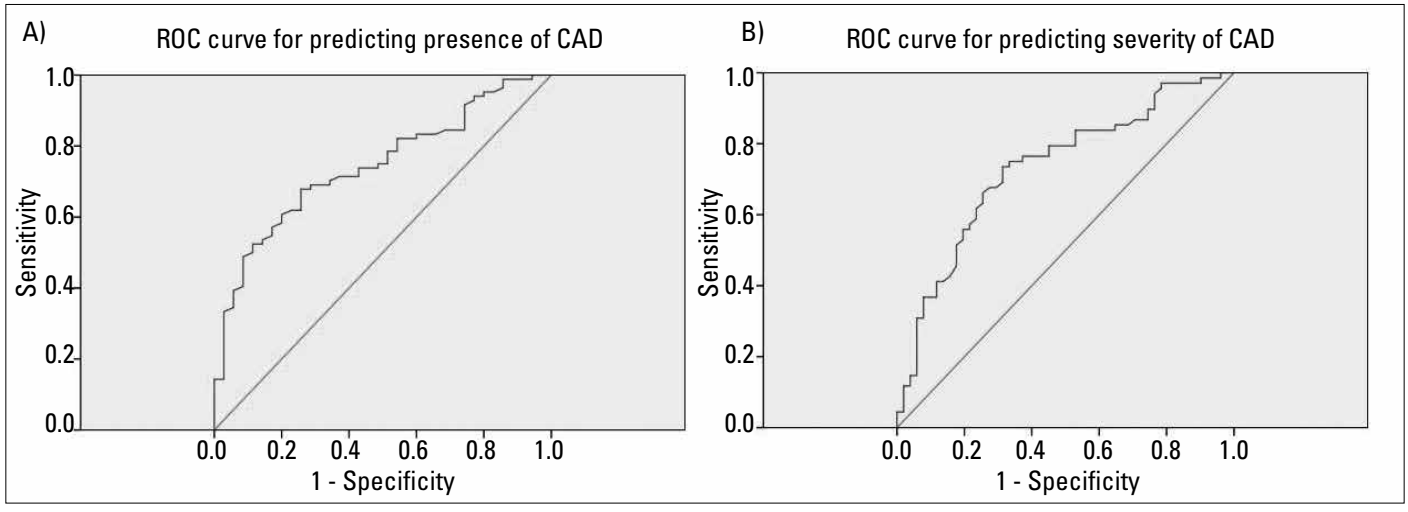

Figure 2. ROC curve analysis of FT3 levels predicting presence (AUC: 0.744, 95% CI: 0.653-0.834, p<0.001) and severity of CAD (AUC: 0.733, 95% CI: 0.642-0.824, p<0.001)
CAD - coronary artery disease, FT3 - free triiodothyronine

Table 3. Predictors of severity of CAD by logistic regression analysis

Variables	Odds ratio (95% CI)	p
FT3, pmol/L	0.238 (0.083-0.685)	0.008
Age, years	1.041 (0.992-1.091)	0.101
Male, n (%)	0.260 (0.069-0.976)	0.046
Total cholesterol, mg/dL	1.000 (0.967-1.033)	0.979
LDL, mg/dL	1.004 (0.964-1.047)	0.832
HDL, mg/dL	0.919 (0.858-0.984)	0.015
Creatinine, mg/dL	0.918 (0.394-2.140)	0.167
Glucose, mg/dL	1.002 (0.989-1.014)	0.078
Ejection fraction, %	0.983 (0.932-1.036)	0.520

FT3 - free triiodothyronine, HDL - high density lipoprotein, LDL - low density lipoprotein

euthyroid patients. Also, the serum FT3 levels were significantly correlated with the Gensini score. Moreover, our study has shown that FT3 predicted the presence (69% sensitivity and 71% specificity) and severity (75% sensitivity and 67% specificity) of CAD in euthyroid patients.

FT4 is a pro-hormone, which is converted to the biologically active FT3 on release from the thyroid gland. FT3 is the most biologically active one among the thyroid hormones and affects almost every process in the body including the temperature, growth and heart rate. Thus, FT3 gives a more accurate measure of the thyroid activity and it is used to detect both hyper- and hypothyroidism (15, 16). An abnormal thyroid hormone metabolism may lead to different forms of heart disease. Hypothyroidism, in particular, is a well-known cause of coronary atherosclerosis (1).

The underlying mechanisms that may influence the relationship between the variations in thyroid function and cardiovascular disease may also have an effect on the relaxation of smooth muscle cells (17), inhibition of collagen-induced platelet aggregation (18), endothelial function, blood rheology (19), and hypercoagulability (20). Subclinical hypothyroidism may be associated with hypertension, hypertriglyceridemia, and elevated total cholesterol/HDL cholesterol ratio. Overt hypothyroidism may result in accelerated atherosclerosis and CAD, presumably because of the associated hypertension, hypercholesterolemia, and hyperhomocysteinemia (21).

Several studies have pointed out a relationship between the serum thyroid hormone levels and the development of atherosclerosis in different populations. Tatar et al. (7) showed that serum FT3 levels were inversely correlated with carotid atherosclerosis and low serum FT3 levels were an important determinant of carotid atherosclerosis. Coceani et al. (22) reported that serum FT3 levels were inversely correlated with the presence of CAD and the low T3 syndrome conferred an adverse prognosis, even after adjusting for the traditional coronary risk factors. Peters et al. (8) examined thyroid functions in a total of 1049 patients immediately following emergency medical admission. They concluded that an elevation in serum FT3 levels at the time of hospital admission was associated with a 2.6-fold greater likelihood of the presence of a coronary event. Moreover, an initially elevated FT3 level is associated with a 3-fold higher risk of developing a subsequent coronary event during the next three years. Excess FT3 was observed as a factor associated with the development and progression of acute myocardial ischemia. Similar to the previous studies, the present study has also revealed a relationship between low serum FT3 levels and the presence of coronary atherosclerosis. In addition to the previous studies, we evaluated the severity of CAD using the Gensini score.

Auer et al. (10) have found that a variation of the thyroid function even within the normal range may influence the presence and severity of coronary atherosclerosis. They reported that lower levels of serum FT4 and higher levels of TSH were associated with severe coronary atherosclerosis. Jung et al. (23) showed that serum FT4 levels were associated with the presence and severity of CAD in the Korean population. This study also suggests that elevated serum FT4 levels even within normal range could be a risk factor for CAD. In the current study, the TSH and FT4 were not found to be linked to the presence and severity of the CAD; nevertheless, the previous studies have not applied the Gensini scores to grade the severity of the CAD.

Various studies have observed different associations between atherosclerosis and the serum thyroid hormone levels within the normal range in euthyroid patients. Some studies have found a relationship between the FT4 and TSH levels and the presence or severity of the CAD (10-11, 23), whereas others demonstrated a similar relationship with FT3 (7, 8, 22). It is possible that differences in sample sizes, study populations, various ethnic groups and laboratory methods will result in these discrepancies.

Study limitations

The main limitation of this cross-sectional study is the limited number of the study subjects. The heterogeneity of the study subjects with respect to anginal classification and ejection fraction may also be considered as a limitation. Coronary angiography provides information about the arterial lumen. Thus, it is not an ideal technique to quantify the overall atherosclerotic burden. Since no causal relationship could be established between the thyroid function and CAD in our study, we can only suggest an association.

Conclusion

The present study demonstrated that serum FT3 concentrations within the normal range are inversely correlated with the presence and severity of CAD in patients referred for coronary angiography. Moreover, serum FT3 concentrations are also correlated with the Gensini score and independently predict the presence and severity of CAD in euthyroid angina patients. In contrast to FT3, thyroid stimulating hormone and FT4 were not observed to be associated with the presence and/or severity of CAD in our population. The FT3 levels may be used to predict an increased risk for CAD. Further studies on a larger number of patients are needed to confirm the relationship between the thyroid function and CAD.

Conflict of interest: None declared.

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