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Association between subclinical hypothyroidism and coronary artery disease

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Summary. Coronary artery disease (CAD) is a common health problem with high morbidity and mortality. In recent years overt hypothyroidism is shown as an independent risk factor of CAD. Thyroid hormones have more effects on the cardiovascular system, and both hypothyroidism and hyperthyroidism have harmful effects on the cardiovascular systemç Subclinical hypothyroidism (SCH) is a common clinical situation with 4-20% frequency. SCH is associated with endothelial dysfunction, coronary atherosclerosis, and cerebrovascular disease. SYNTAX score is the angiographic scoring system and is widely used to evaluate the severity and complexity of CAD. The aim of this study to evaluate the association between SCH and SYNTAX score. This study is a retrospective cohort of participants who undergo coronary angiography and resulted in coronary artery bypass graft surgery. Participants divided into two group according to their SYNTAX score as high SYNTAX score (SYNTAX ≥ 23) and low SYNTAX score (SYNTAX<23). There is no statistically significant difference between two groups regarding age, male, height, weight, smoking, hypertension, diabetes mellitus, hyperlipidemia, peripheral artery disease, total cholesterol, HDL-C, LDL-C, TG, free thyroxine (fT4), free triiodothyronine (fT3), thyroid stimulating hormone (TSH), and uric acid. Serum LDL, total cholesterol levels are significantly higher in the SCH group than non-SCH group (respectively; p=0.029, p=0.024). There is a positive correlation between SCH and age, SCH prevalence increase with older age (p=0.017). Patients were divided into two group according to their TSH levels as SCH (fT3 and fT4 normal, TSH≥4). We used the SYNTAX score to evaluate the severity of CAD severity. However, there is no significant difference. Further studies are needed to evaluate the association between SCH and CAD.

Keywords: Coronary artery disease, subclinical hypothyroidism, ageing

Introduction

Coronary artery disease (CAD) is a common health problem with high morbidity and mortality risk. The elimination of cardiovascular risk factors such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), smoking and obesity is the important part of cardiovascular disease prevention. In recent years overt hypothyroidism (OH) is shown as an independent risk factor of CAD. Thyroid hormones have more effects on the cardiovascular system, and both hypothyroidism and hyperthyroidism have harmful effects on the heart and vascular system (1). OH is defined as elevated thyroid stimulating hormone (TSH) levels with abnormally T4 levels. Subclinical hypothyroidism (SCH) is a common clinical situation with 4-20% frequency. The most common reason of SCH is autoimmune thyroiditis, and only a small group of patients have symptoms (2,3). SCH is associated with endothelial dysfunction, coronary atherosclerosis, cer-

ebrovascular disease, and defined as elevated (TSH) and normal serum free thyroxine (fT4), free triiodothyronine (fT3) levels (4). This association is thought to be due to several mechanisms such as increased low-density lipoprotein-cholesterol (LDL-C), HT, impaired coagulation mechanism and high C-reactive protein levels (5). Many studies showed a positive correlation with thyroid hormone and serum total cholesterol (TC), LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG) and negative correlation with serum HDL-C (6). Besides that carotid intima-media thickness is found significantly higher in SCH and OH group in previous studies as an indicator of atherosclerosis (7).

There are small clinical studies about thyroid replacement treatment on dyslipidemia and HT. However, there is no clinical data with this therapy and effects on cardiovascular mortality and morbidity (8-10). Even so, recent guidelines suggest thyroid hormone replacement therapy in SCH with special conditions such as pregnancy, infertility, symptomatic patients, high risk of progression to OH. Some of them suggest treating SCH in most patients with a serum TSH level below 10 IU/L (11).

SYNTAX score is used to evaluate CAD complexity and grade. Also for deciding coronary artery bypass surgery (CABG) or percutaneous coronary intervention in patients with serious CAD predicting long-term mortality. It includes anatomical complexity of all coronary arteries and indicates the severity of CAD (12).

On the basis of the possible association between SCH and the presence of atherosclerosis, the aim of this study was to the evaluıate association between more complexity of coronary artery disease and TSH levels.

Materials and Method

Participants

Our study is a retrospective and conducted with cohort of participants who undergo coronary angiography (CA) and resulted with coronary artery bypass graft surgery at Near East Medical Faculty Hospital from September 2015- September 2018. We included patients with the indication of CABG for severe coronary artery disease and were decided with the heart team. Patients with previous coronary artery disease history, thyroid disorder or operation history from thyroid gland and taking thyroid replacement therapy or antithyroid therapy, valve disease and undergo valve surgery at the same time with CABG and admit with acute coronary syndrome (ST-elevation myocardial infarction or non ST elevation myocardial infarction), have liver function abnormalities (serum alanine transaminase >2 times the upper normal limits) or renal insufficiency (serum creatinine >2.0 mg/dL) were excluded from study.

A detailed medical history of each patient was compiled, included the history of DM, HT, HL, peripheral artery disease, smoking, alcohol use, family history of CAD and treatment history. The patients' height and fasting weight were measured, body mass index (BMI) (weight/height in kg/m2) was calculated. Glucose, lipids profile (TC, TG, HDL-C, LDL-C), creatinine levels, white blood cell (WBC), C-reactive protein (CRP), TSH, free T3 and free T4 were assayed in blood samples after 12h overnight fasting. We defined SCH as elevated serum TSH level (TSH≥4 IU/L) with normal levels of fT3 and fT4. Patients were divided into two group according to their TSH levels as SCH (fT3 and fT4 normal, TSH≥3) or not. Blood pressure (BP) was measured using a mercury sphygmomanometer in a sitting position, after 10 minutes of rest.

The study was approved by the local Ethical Committee, and all patients provided written informed consent.

Coronary angiography

We performed CA using the Judkins technique through the femoral or radial artery. Each coronary artery was visualised in at least 2 different plane images. According to baseline CA, the SYNTAX score was calculated for all patients by two experienced interventional cardiologists unaware of the patients' clinical or laboratory results. SYNTAX score was determined for all coronary lesions with > 50% diameter stenosis in a vessel > 1.5 mm based on SYNTAX score calculator 2.1 (www.SYNTAXscore.com). Patients were divided into two groups as high SYNTAX score (≥ 23) or low SYNTAX score (<23).

Statistical analysis

Statistical analysis was performed using the SPSS (version 20.0, SPSS Inc., Chicago, Illinois) software package. Continuous variables were expressed as the mean ± standard deviation (mean± SD), and categorical variables were expressed as a percentage (%). The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Student's t-test was used to evaluate continuous variables showing normal distribution, and Mann-Whitney U-test was used to evaluate variables that did not show normal distribution. A p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Five of participant excluded because of the missing data, 124 of them were included in the analysis. Participants divided into two group according to their SYNTAX score as high SYNTAX score (SYNTAX ≥23) and low SYNTAX score (SYNTAX<23).

There is no statistically significant difference between two groups regarding age, male, height, weight, BMI, smoking, HT, DM, HL, PAH, TC, HDL-C, LDL-C, TG, fT3, fT4, TSH, and uric acid (Table 1).

Baseline characteristics of the randomised patients in SCH and non SCH group are listed in Table 2. 6.8% of them comprising SCH (n=8), 86.8% (n=112) of patients were male, 13.2% (n=17) of them female between 45 and 90 years. Serum LDL, total cholesterol levels are significantly higher in the SCH group than non-SCH group (respectively; p=0.029, p=0.024) (Table 2). There is a positive correlation between SCH and age, SCH prevalence increase with older age (p=0.017). There is no statistically significant difference between SCH and SYNTAX score (p=0.724).

Table 1. Comparison of basal demographics features in SYNTAX groups

Variable	SYNTAX score ≥23 (n=56)	SYNTAX score <23 (n=73)	p-value
Age (year)	65.8	66.3	0.780
Male (n)	51	61	0.211
Height (cm)	169.2	169.7	0.769
Weight (kg)	81.6	84.6	0.296
Smoking (n)	20	24	0.736
Hypertension (n)	40	56	0.495
Hyperlipidemia (n)	17	19	0.587
Diabetes mellitus (n)	23	26	0.527
PAH (n)	6	7	0.833
TC (mg/dl)	194.3	195.5	0.893
LDL-C (mg/dl)	115.0	123.3	0.297
HDL-C (mg/dl)	37.3	40.1	0.114
TG (mg/dl)	213.2	161.2	0.234
FT3 (pg/ml)	2.5	2.6	0.442
FT4 (pg/ml)	1.1	1.0	0.423
TSH (mIU/ml)	1.6	1.7	0.696
Uric acid (mg/dl)	6.3	6.2	0.838

BMI, body-mass index; PAH, peripheral artery disease; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormon

Table 2. Comparison of basal demographics features between SCH and non-SCH groups.

Variable	SCH (n=8)	Non-SCH (n=116)	p value
Age (years)	8	116	0,017
Male (n)	5	103	0,066
Height (cm)	168,8	169,5	0,858
Weight (kg)	89,4	83,3	0,340
Smoking (n)	3	40	1,0
Hypertension (n)	6	87	1,0
Hyperlipidemia (n)	1	35	0,436
Diabetes mellitus (n)	3	45	1,0
PAH (n)	1	11	0,568
TC (mg/dl)	230,8	189,9	0,024
LDL-C (mg/dl)	151,2	115,3	0,029
HDL-C (mg/dl)	41,8	37,9	0,373
TG (mg/dl)	189	185	0,967
FT3 (pg/ml)	2,54	2,60	0,722
FT4 (pg/ml)	1,07	1,06	0,974
SYNTAX score (≥23)(%)	21,8	23,1	0,263
Uric acid (mg/dl)	6,07	6,30	0,775

BMI, body-mass index; PAH, peripheral artery disease; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; FT3, free triiodothyronine; FT4, free thyroxine

Discussion

We used SYNTAX score to evaluate the severity of CAD and aim to show a correlation between SCH and CAD severity, however, there is no significant association between serum TSH level and SYNTAX score. Also, SCH and non SCH prevalence are similar between high and low SYNTAX score group. SYNTAX score indicates the anatomical structure and quality of coronary vessels, besides that complexity of the CAD. It is found associated with cardiovascular morbidity and mortality (13-21). In previous studies SCH is found an independent risk factor for CAD in groups without previous CAD. In our study participants have already multivessel CAD and they underwent CABG. Therefore SCH is not found associated with the CAD complexity and severity.

Hypothyroidism is a significant health problem due to its high prevalence and associated risks of atherosclerosis, endothelial dysfunction and weight gain. It's well known that there is a strong association between CAD and OH. Dyslipidemia is considered for the main mechanism of increased atherosclerosis risk in OH (22). In the same manner, in our study serum total, cholesterol and LDL levels are found significantly higher in the SCH group than the non-SCH group. Also, patients with SCH are older than the non-SCH group. The other mechanisms which are thought to be responsible are obesity, arterial stiffness, hypercoagulability and endothelial dysfunction (22-25). Desai et al. (26) demonstrated the association with OH and cardiovascular comorbidities and complications, all-cause mortality in hospital after percutaneous coronary intervention.

Although previous studies showed a correlation between SCH and coronary atherosclerosis some of them did not confirm it (27-29). It is reported that SCH increases the risk of atherosclerosis and cardiovascular system disease with a similar mechanism as OH (30). SCH is defined as mild (TSH<10 IU/L) or severe (TSH ≥10 IU/L). In previous studies, SCH and cardiovascular disease link were shown especially in a group with TSH levels ≥ 10 μIU/ml (31). In our study mean TSH levels in the SCH group was lower than 10 IU/L, we exclude the severe SCH because of the perioperative and postoperative risks of CABG. The insignificant results of our study may be due to study inclısion criteria. Also, Lee et al. (32). showed that repeat PCI risk is higher in SCH than euthyroid patients for in-stent restenosis, but there is no difference for de-novo lesions.

TSH level increases with ageing, and there is no consensus about the harmful effects of SCH. It is thought to be a compensatory mechanism and may have beneficial or neutral effects in the elderly population (33). It may have resulted in an underestimation of SCH in the elderly population. Rodondi et al. (34) showed a positive correlation between cardiovascular mortality/morbidity and SCH. On the other hand, other studies with elderly population did not demonstrate association between cardiovascular risk and SCH (35).

There is no consensus about the TSH criteria for the SCH definition. Previous studies defined SCH as TSH>4 IU/L although some of them accept TSH>5 IU/L, this may result in a misclassification and underestimation of SCH. We defined SCH as TSH>4 IU/L however, SCH prevalence is 6.8%, and there is no association with severity of coronary artery disease.

Conclusion

The coexistince of OH and CAD is known for many years. In the light of this findings we aim to evaluate the association between the SCH and CAD severity, however, there is no significant association. Further studies are needed to evaluate the association between SCH and SYNTAX score.

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