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Impact of subclinical hypothyroidism on clinical outcomes following percutaneous coronary intervention☆

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ABSTRACT

Background: Similar to overt hypothyroidism, subclinical hypothyroidism (SCH) has been reported to increase the risk of cardiovascular disease. However, the influence of SCH on clinical outcomes following percutaneous coronary intervention (PCI) remains unclear.
Methods: We performed a prospective cohort study. SCH was defined as a thyroid-stimulating hormone (TSH) level ≥4.5 mIU/l and a normal level of free thyroxine (FT4). A composite event was defined as the combination of cardiac death, non-fatal myocardial infarction (MI) and repeat revascularization.
Results: Of 936 patients, who were observed for 3.1 years, 100 patients (10.7%) were diagnosed with SCH. Repeat revascularization, cardiac death and a composite event occurred more frequently in the SCH group than in the euthyroidism group, while the incidence of non-fatal MI was similar between the two groups. Multiple Cox regression analysis showed that SCH was associated with the risk of a composite event (hazard ratio, 1.52; 95% confidence interval, 1.04–2.22) after adjustment for age, sex, current smoking, ST-segment elevation MI, prior PCI, diabetes, hypertension, renal function, left ventricular ejection fraction, B-type natriuretic peptide, stent numbers, total stent length, stent types, obesity and lipid profiles. Serum TSH levels were also significantly associated with the risk of a composite event. SCH was not associated with repeat PCIs for *de novo* stenotic lesions but was associated with repeated PCIs for in-stent restenotic lesions.
Conclusions: SCH negatively impacted clinical outcomes following PCIs. Therefore, patients with SCH should be carefully observed after undergoing a PCI.

1. Introduction

Subclinical hypothyroidism (SCH) is a common clinical condition with a prevalence of 4–20% in the general population. SCH presents with few or no symptoms or signs of hypothyroidism but features a slightly elevated serum thyroid-stimulating hormone (TSH) level [1,2]. Although the serum levels of free thyroxine (FT4), the active hormone, are typically within the reference range, several studies have reported increased cardiovascular risk and mortality in SCH patients [3,4]. Subclinical atherosclerotic disorders, such as coronary artery calcification, carotid intima-media thickening and atheroma, are more prevalent in SCH [5,6]. Endothelial dysfunction, impaired cholesterol metabolism and increased C-reactive protein (CRP) levels have also been reported to be associated with SCH [7–9] and to affect clinical outcomes following percutaneous coronary interventions (PCIs). However, whether SCH is associated with cardiovascular events and death in patients undergoing PCIs remains uncertain [10]. Therefore, we investigated the differences in clinical outcomes following PCIs between patients with normal TSH levels and patients with SCH in a prospective clinical cohort study.

2. Methods

2.1. Patients

A prospective PCI registry has been operated in the Department of Cardiology, Hanyang University Hospital, Seoul, Republic of Korea since 2009 to evaluate the clinical outcomes and safety of PCIs [11]. Patients undergoing coronary angiography in the center were consecutively enrolled in the registry. Written informed consent was obtained from all patients before enrollment. The Hanyang University Hospital Institutional Review Board approved the protocol and monitored registry operation.

Patients in the registry who underwent PCI with simple balloon angioplasty or stent implantation between March 2010 and December 2013 were consecutively enrolled in this study. Patients who had previously undergone coronary artery bypass surgery were excluded, as were patients who suffered from debilitating conditions including advanced malignancies, advanced liver cirrhosis, severe autoimmune diseases and cerebrovascular accidents with major sequelae. Information regarding demographic characteristics, past medical histories and social histories was obtained. Body weights, heights, and waist circumferences were determined on the day before or within 7 days after index PCI. Lipid profiles, serum glucose levels and hemoglobin A1c levels were measured after an 8-h fast the morning before or following the index PCI. Serum highly sensitive CRP

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(hsCRP) and B-type natriuretic peptide (BNP) levels were measured before the index PCI. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Diseases study equation and chronic kidney disease was defined as an eGFR ≤60 ml/min/1.73 m^2. Before the procedure, 300 mg of aspirin and P2Y12 inhibitors (600 mg of clopidogrel, 60 mg of prasugrel, or 180 mg of ticagrelor) were administered to all patients. After the index PCI, all patients received dual antiplatelet agent therapy for at least 1 year and high-intensity statin therapy, regardless of their low-density lipoprotein (LDL) cholesterol serum levels, unless there were contraindications to statin use. Lipid profiles were repeated between 3 and 12 months after index PCI to assess lipid control status. Echocardiography was performed in all patients at least 3 months before or after the index PCI to measure left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI) and mitral early inflow velocity to mitral annulus velocity ratio (E/E′). In patients with acute coronary syndrome (ACS), an echocardiography was usually performed within 24 h before or within 7 days after the index PCI.

2.2. Thyroid function tests and the definition of SCH

Serum TSH and FT4 levels were measured before the index PCI. Patients whose TSH and FT4 levels had been measured after any radiologic test using contrast media or had not been measured were excluded. Euthyroidism (ET) was defined as a TSH level (0.4–4.4 mIU/l) and an FT4 level (0.7–1.8 ng/dl) within the indicated normal ranges [12]. SCH was defined as an increased TSH level (≥4.5 mIU/l) and a normal FT4 level, without symptoms or signs of hypothyroidism [1]. Patients who presented with a decreased TSH level (<0.4 mIU/L) or an abnormal FT4 level, patients who had been diagnosed with overt hypothyroidism or hyperthyroidism and patients who were taking anti-thyroid drugs or thyroid hormone replacement (THR) therapy were excluded.

2.3. PCI and clinical outcomes

PCI was performed using standard techniques. The diameter of each stenotic lesion was compared with the luminal diameters of normal vessel segments, located both proximal and distal to the lesion. A stenotic lesion that required PCI was defined as a lesion with a luminal narrowing ≥70% based on quantitative angiographic measurements. During the observation period, repeat coronary angiography was performed when patients presented with symptoms of angina or signs of myocardial ischemia. Standardized definitions of clinical events that are frequently used in cardiovascular trials were used in this study, as described by Hicks et al. [13]. The detail definitions were described in Ref [14]. The first clinical event that occurred after the index PCI was used as the patient's clinical event. A composite event was defined as the combination of repeat revascularization, non-fatal myocardial infarction (MI) and cardiac death. PCIs for *de novo* stenotic lesions in non-target coronary arteries were not considered repeat revascularizations. In-stent restenosis (ISR) was defined as a re-narrowing >50% at a previously stented site and at the adjacent vascular segments 5 mm proximal and distal to the site. Repeat PCI was defined as a PCI that was performed for any causes after the index PCI.

2.4. Statistical analyses

Patients were divided into two groups: the ET group and the SCH group. The SCH group was subdivided into two groups: SCH group 1 (mildly elevated TSH levels ranging from 4.5–6.9 mIU/l) and SCH group 2 (moderately elevated TSH levels ≥7.0 mIU/l). Student's *t*-tests and Chi-square tests were employed for continuous variables and categorical variables, respectively. Mann-Whitney *U* tests were employed for variables with skewed distributions. Kaplan-Mayer survival analysis with a log-rank test was used to compare event-free survival rates between the two groups. To better understand the relationship between TSH levels and the risk of the composite event, we compared the hazard rates in groups of 19 to 40 patients with consecutive TSH levels with those in the ET group. Because the median TSH level in the ET group was 1.78 mIU/l, the lowest TSH level of each group was a regular sequence from 2.0 to 10.0 mIU/l with an increment of 0.5 mIU/l. The patients in one group were not exclusive to those in neighboring groups, and the numbers of patients in the groups varied because patients were more sparsely distributed in high TSH levels. To evaluate the nonlinear relationship between the risk of the composite event and TSH levels, Cox regression analysis with a restricted cubic spline function for TSH levels was employed. Multiple numbers of knots (3 to 12) were tested for the restricted cubic spline model until C-statistic of the model reached the ceiling. The best-fit nonlinear regression model was compared with a linear model using an Analysis of Deviance. To evaluate the independent associations between SCH and adverse clinical outcomes, multiple Cox regression analyses were performed with all relevant covariates. Detail methods for the Cox regression analysis are described in Ref [14]. All statistical analyses were performed using statistical software R-3.4.0 and $p < 0.05$ was considered significant.

3. Results

3.1. Baseline and angiographic characteristics

A total of 936 patients were enrolled in the study. The median TSH level was 1.95 mIU/l, and the average FT4 level was 1.15 ± 0.19 pmol/l. SCH was identified in 100 patients (10.7%). Baseline and angiographic characteristics of patients are presented in Table 1. There were no significant differences in demographic characteristics, social and past medical histories or peri-procedural medications between the ET and SCH group, except for the fact that ST-segment elevation MI (STEMI) was more frequent in the SCH group than in the ET group. Hemoglobin levels were lower and BNP levels were higher in the SCH group than in the ET group. However, there were no other baseline differences in laboratory tests results between the two groups. LDL cholesterol (−27.9 mg/dl, $p < 0.001$) and triglyceride levels (−9 mg/dl, $p < 0.001$) decreased and HDL cholesterol levels (+1.2 mg/dl, $p = 0.006$) slightly increased in the entire cohort compared with the lipid profiles at baseline, whereas there were no differences in lipid profile changes between the two groups. LVEF was slightly lower and the frequency of LVEF ≤50% was higher in the SCH group, whereas LVMI and E/E′ did not differ between the two groups. All angiographic characteristics were similar between the two groups.

3.2. Clinical outcomes following PCI and SCH

The median observation duration was 490 days (3–1134 days). Cardiac death, non-fatal MI, repeat revascularization and the composite event occurred in 13 (1.4%), 30 (3.2%), 152 (16.2%) and 195 (20.8%) patients, respectively. Repeat revascularization, cardiac death and the composite event occurred more frequently in the SCH group than in the ET group, while the incidence of non-fatal MI was not different between the two groups (Fig. 1A). Because 11 of the 13 cardiac deaths resulted from fatal MI, the combined event of fatal and non-fatal MI was more frequent in the SCH group than in the ET group (9% *vs.* 3.8%, $p = 0.017$ in a log-rank test). Although the composite event rate appeared to increase with TSH level cut-off values, the difference in the event rate between patients with a TSH level ≥ 4.5 mIU/l and patients with a TSH level ≥ 7.0 mIU/l was not significant. When the SCH group was divided into two groups, a group with mild TSH elevation (SCH group 1, TSH 4.5–6.9 mIU/l) and a group with moderate TSH elevation (SCH group 2, TSH ≥7.0 mIU/l), there was no difference in the composite event rate between the ET group and SCH group 1. However, the composite event rate was higher in SCH group 2 than in the ET group and marginally higher in SCH group 2 than in the SCH group 1 (Fig. 1B).

3.3. The risk of the composite event and serum TSH levels

Multiple Cox regression analysis revealed that SCH was a significant predictor of the composite event along with diabetes mellitus, total stent length (TSL), a past history of PCI, a lower BMI and second-generation DES. When SCH was stratified into the above two groups, SCH group 2 remained a significant predictor of the composite event, whereas SCH group 1 was no longer associated with the risk of a composite event (Table 2). The hazard ratios of the composite event derived from the groups of patients with consecutive TSH levels increased with the corresponding median TSH levels of the groups when the median TSH levels ranged from approximately 3 to 8 mIU/l and then plateaued. A Cox regression model using a restrictive cubic spline function (knot = 10) showed a similar pattern regarding the relationship between the hazard ratios and TSH levels and a better goodness of fit than the linear model (Fig. 2).

3.4. Subgroup analyses

Subgroup analysis showed that SCH was associated with a composite event in patients without MI/STEMI, patients in whom second-generation DESs were implanted and patients with prior PCI, a TSL < 38 mm, single-vessel coronary artery disease (CAD), diabetes mellitus, a BMI ≥25 kg/m^2, hsCRP ≥1.0 mg/dl and LDL reduction <26 mg/dl. Significant or marginally significant interactions of MI ($p = 0.054$), prior PCI ($p < 0.001$), TSL < 38 mm ($p = 0.093$) and single-vessel CAD ($p = 0.075$) were found