Do Percutaneous Coronary Interventions of Chronic Total Occlusion Have a Different Impact on Thyroid Functions Compared to Non-Complex Percutaneous Coronary Interventions?

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Short Title: Thyroid Dysfunction After PCI of Coronary CTO

Key Words: Coronary occlusion · Contrast media · Percutaneous coronary intervention · Thyroid diseases
Highlights of the study

- The present study demonstrated that percutaneous coronary intervention for coronary chronic total occlusion lesions increased the risk of overt hyperthyroidism in patients with subclinical hyperthyroidism at baseline compared to percutaneous coronary intervention for non-complex coronary lesions.

- No significant risk was observed in euthyroid patients.
Abstract

Objective: This study assessed whether high levels of iodide administered during percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) differentially influenced thyroid function compared to PCI for non-complex coronary lesions. Subjects and Methods: A total of 615 patients, 205 of whom underwent elective PCI for CTO lesions (Group I) and 410 of whom underwent elective, non-complex PCI, including non-CTO, non-bifurcation, non-calcified and non-tortuous (Group II) were enrolled in the study. Patients were monitored for development of incidental thyroid dysfunction between one and six months after PCI. Results: Patients in Group I was administered a median of 255 mL of contrast medium during PCI for CTO, whereas a median of 80 mL of contrast medium was administered to patients in Group II during non-complex PCI ($p = 0.001$). Ten (5.4%) of the 186 euthyroid patients in Group I developed subclinical hyperthyroidism, while 19 (5%) of the 379 euthyroid patients in Group II developed subclinical hyperthyroidism ($p = 0.854$). However, 7 (50%) of the 14 subclinical hyperthyroid patients in Group I developed overt hyperthyroidism, whereas 3 (12%) of the 25 subclinical hyperthyroid patients in Group II developed overt hyperthyroidism ($p = 0.019$).

Conclusion: In euthyroid patients, PCI for coronary CTO lesions did not increase the risk for subclinical hyperthyroidism compared to PCI for non-complex coronary lesions. However, in patients with subclinical hyperthyroidism at baseline, PCI for coronary CTO lesions significantly increased the development of overt hyperthyroidism compared to PCI for non-complex coronary lesions.
**Introduction**

Exposure to iodinated contrast media (ICM) is frequent in daily medical practice, particularly due to the four- to eight-fold increase in computed tomography (CT) and cardiac catheterization over the past two decades [1]. An iodine-containing contrast medium of 100 mL contains 3500 µg of free iodide, 22.5 times the recommended daily intake. These high levels of iodide might suppress thyroid hormone synthesis (Wolff-Chaikoff effect) or cause hyperthyroidism (Jod-Basedow phenomenon) [2]. The prevalence of ICM-induced thyroid dysfunction remains under-researched. ICM-induced thyroid dysfunction incidence ranges from 0.05 to 5% and is more common in patients with pre-existing thyroid disease [3].

Coronary chronic total occlusion (CTO) is defined as TIMI grade 0 flow (no flow) in the occluded segment of a coronary artery persisting for more than three months [4]. Revascularization of coronary CTOs is a significant component of contemporary interventional cardiology. In the early 2000s, the procedural success rate was around 65-70%, but it has since increased to up to 90% in the last decade due to improvements in technology and techniques and at the expense of increased costs, procedure, fluoroscopy times, and ICM exposure over non-CTO percutaneous coronary intervention (PCI) [5-8].

Whether PCI increases the risk of thyroid dysfunction is an important question because even subclinical thyroid dysfunction can negatively affect the cardiovascular system [9-12]. This study thereby evaluates whether the much higher levels of ICM administered during PCI for CTO may differentially influence thyroid function as compared to PCI for non-complex coronary lesions such as non-CTO, non-bifurcation, non-calcified and non-tortuous.

**Subjects and Methods**

*Study Design and Patient Population*

This observational, retrospective cohort study was carried out on patients who visited a tertiary referral centre in an iodine-deficient area of Sakarya, Turkey, between July 2015 and
December 2017. A flowchart of patient enrolment is shown in Figure 1. Group I comprised 205 patients who underwent PCI for CTO lesions. All Group I participants were routinely assessed for thyroid function before the coronary procedure and reassessed from one to six months after the procedure. Group II contained a pool of 410 patients who underwent elective, non-complex PCI within the same time period. These participants were also assessed for thyroid function before and one to six months after non-complex PCI. None of the patients in either group had a history of thyroid disease, nor had they used an antithyroid drug or thyroid replacement medication. Patients newly diagnosed with subclinical hypo- or hyperthyroidism during the pre-procedural assessment and who had not used any antithyroid or thyroid replacement medication were included in the study. This study complies with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee.

**Thyroid Function Tests**

Serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) levels were measured using an Access 2 Immunoassay System (Beckman Coulter, USA). Normal ranges for TSH, FT4, and FT3 values are 0.34 to 5.86 IU/mL, 0.61 to 1.12 ng/dL, and 2.5 to 3.9 pg/mL, respectively. These values were measured before and one to six months after the procedure. A decrease in TSH below the assay reference range with a normal FT4 and FT3 was considered subclinical hyperthyroidism, and an increase in FT4 and FT3 above the assay reference range in addition to suppressed TSH in patients with clinical symptoms was considered overt hyperthyroidism. An increase in TSH above the assay reference range with a normal FT4 and FT3 was considered subclinical hypothyroidism, while a decrease in FT4 and FT3 below the assay reference range accompanied by an elevated TSH in patients with clinical symptoms was considered overt hypothyroidism.

**Coronary Angiography and Iodinated Contrast Media**
All cardiovascular procedures were performed using a Toshiba Infinix 8000V or Infinix
8000G5 (Toshiba Medical Systems, Nasushiobara, Japan). The ICM used in the study was
iohexol (Omnipaque®, 300 mg iodine/mL, GE Healthcare, USA), a low osmolar and non-ionic
ICM.

Statistical Analysis

Data analyses were performed with the Statistical Package for Social Sciences (SPSS)
version 24 for Windows (SPSS Inc, Chicago IL, USA). The Student’s t-test and Mann-Whitney
U test were used to compare means and medians in the two groups. The Chi-square test or
Fisher’s exact test, where appropriate, was used to compare proportions and percentages in the
groups. The correlation of age to changes in TSH after ICM exposure was calculated with the
Pearson test. A p-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of study participants are presented in Table 1. No differences
were observed between groups other than age and extent of ICM exposure. The mean ages of
Groups I and II were 60.9 and 62.7, respectively (p = 0.042). The patients in Group I were
administered a median of 255 mL (interquartile range: 195–300 mL) of ICM during CTO PCI,
whereas a median of 80 mL (interquartile range: 65–90 mL) of ICM was delivered to those in
Group II (p < 0.001); this difference was found to be statistically significant. Post-procedural
thyroid function tests were conducted between one and six months after ICM exposure. The
median time for post-procedural thyroid function tests in Group I was 147 days (4.9 months)
and that for Group II was 152 days (5.1 months). There was no statistically significant
difference in the median date of post-procedural thyroid function tests between the two groups
(p = 0.197).

In Group I, 186 patients (90.8%) were euthyroid, 14 patients (6.8%) had subclinical
hyperthyroidism, and 5 patients (2.4%) had subclinical hypothyroidism at baseline. In Group
II, 379 patients (92.4%) were euthyroid, 25 patients (6.1%) had subclinical hyperthyroidism, and 6 patients (1.5%) had subclinical hypothyroidism at baseline. Of the 186 euthyroid patients in Group I, 10 (5.4%) developed subclinical hyperthyroidism after PCI, whilst 19 (5%) of the 379 euthyroid patients in Group II developed subclinical hyperthyroidism, a difference that was not statistically significant ($p = 0.854$). However, 7 (50%) of the 14 subclinical hyperthyroid patients in Group I developed overt hyperthyroidism after PCI, whereas only 3 (12%) of the 25 subclinical hyperthyroid patients in Group II developed overt hyperthyroidism ($p = 0.019$). None of the euthyroid patients in Group I developed subclinical hypothyroidism, whereas 2 (0.5%) of the euthyroid patients in Group II developed subclinical hypothyroidism, a difference that was not statistically significant ($p = 1.000$) (Table 2). None of the patients in either group with subclinical hypothyroidism at baseline developed overt hypothyroidism (Fig. 2).

Age was the only parameter that varied significantly between groups. In the univariate analysis, however, changes in TSH values after ICM exposure as calculated by subtraction of post-procedural TSH from pre-procedural TSH were not associated with age ($p = 0.557$).

**Discussion**

While a few studies have investigated the influence of ICM after coronary angiography on thyroid function [13 - 15], to the best of our knowledge, there has not yet been an evaluation of the effect of extremely supraphysiological levels of iodide administered during PCI for coronary CTO on thyroid function. PCI for coronary CTO lesions is a complex and more technically demanding procedure that results in increased total procedure and fluoroscopy times, enhanced costs, and greater ICM exposure. This procedure may thus have a more pronounced effect on thyroid function than a standard, non-complex PCI. In this study, euthyroid, subclinical hyperthyroid and subclinical hypothyroid patients were enrolled.
Under normal physiological conditions, active transport of iodine into the thyroid gland via the sodium-iodine symporter is stimulated by TSH [16]. The subsequent synthesis and release of FT4 and FT3 are tightly regulated by the thyroid gland. In susceptible individuals, however, exposure to supraphysiological levels of iodide may overcome these regulatory processes and lead to hypothyroidism (Wolff-Chaikoff effect) or hyperthyroidism (Jod-Basedow phenomenon) [13,17 - 20]. Exposure to excess iodine results in a transient decrease in thyroid hormone synthesis due to an acute Wolff-Chaikoff effect. In rats undergoing persistent excess iodine exposure, thyroid function returned to normal levels within 24 to 48 hours, known as escape from acute Wolff-Chaikoff effect [21]. In humans, TSH levels peaked at 3 to 5 days and decreased gradually thereafter [20]. Belloni et al. found that intravenous ICM in children with congenital heart disease resulted in a decrease in TSH levels after 48 hours of CT, but returned to within normal limits by discharge [22]. Escape from acute Wolff-Chaikoff effect occurring after 8 to 10 days has also been observed [23]. In the present study, thyroid function was only re-evaluated after more than one month, which could explain why iodine-induced hypothyroidism was only observed in two of our patients.

It has been demonstrated that ICM exposure causes incidental hyperthyroidism [13,17 - 19]. The present study recapitulated these findings, with ICM exposure resulting in incidental hyperthyroidism in approximately 5% of patients from both groups; however, there was no statistical difference regarding the development of subclinical hyperthyroidism among euthyroid patients from either group despite the increased amount of ICM used in Group I. Results from the present study suggest that PCI for coronary CTO lesions does not increase the risk of development of subclinical hyperthyroidism over PCI for non-complex coronary lesions in euthyroid patients. However, progression to overt hyperthyroidism was significantly higher for patients with subclinical hyperthyroidism at baseline in Group I than in such patients in Group II. This indicates that the higher doses of ICM during PCI for coronary CTO increase
the risk of overt hyperthyroidism in patients with subclinical hyperthyroidism at baseline, but not in patients with normal thyroid function. No published reports have addressed this discrepancy thus far.

In the literature, study populations exposed to ICM were virtually all euthyroid at baseline; studies on patients with subclinical hyper- or hypothyroidism are scarce [14]. No article has yet focused on patients with subclinical hyperthyroidism who were then exposed to ICM, and the rate of development of overt hyperthyroidism remains unknown in this population. Findings from the current study demonstrate a high rate of development of overt hyperthyroidism in patients with subclinical hyperthyroidism at baseline for both PCI for CTO and non-complex PCI. This could be explained by patients with subclinical hyperthyroidism potentially presenting with untreated Graves’ disease, multinodular goitre or thyroid autonomy, and suggests that physicians need to be more careful in performing PCI, particularly for CTO, on patients with subclinical hyperthyroidism at baseline, as our data indicate an increased risk for developing overt hyperthyroidism in this cohort. A recent update to contrast media safety recommended that patients consult an endocrinologist before undergoing any procedure with ICM to uncover subclinical thyroid dysfunction such as untreated Graves’ disease, multinodular goitre, or thyroid autonomy, to reduce the likelihood of thyrotoxicosis [24]. Further studies are needed to delve into the incidence of overt hyperthyroidism in patients with subclinical hyperthyroidism after exposure to ICM in more depth and determine whether prophylaxis or pre-treatment could mitigate thyroid dysfunction after an ICM procedure.

In the present study, patients had a post-procedural thyroid function test between one and six months after ICM exposure, with a median of five months. Existing studies have also demonstrated an increased incidence of hyperthyroidism in the months following ICM [2,17,19,25,26]. This time interval was specifically addressed in monitoring the development of incidental hyperthyroidism post-ICM in this study.
This study has some limitations. First, this report details a retrospective, single-centre study. Second, all patients in the present study were only assessed for biochemical parameters. An ultrasonographic examination of the thyroid gland to measure gland volume and check for nodular lesions prior to ICM may have ascertained which patients were at an increased risk of thyroid dysfunction development. Third, post-procedural thyroid function was re-evaluated only once at a median of five months after the ICM exposure and did not assess variations immediately following ICM exposure that may have presaged clinical thyroid dysfunction. Fourth, only a limited number of patients presented with subclinical hyperthyroidism in this study. Further studies focusing on the influence of ICM on thyroid function in patients with subclinical hyperthyroidism at baseline are needed.

**Conclusion**

The present study demonstrated that PCI for coronary CTO lesions did not increase the risk of development of subclinical hyperthyroidism as compared to PCI for non-complex coronary lesions in euthyroid patients; however, a significantly increased risk for overt hyperthyroidism was observed for patients with subclinical hyperthyroidism at baseline. Cardiologists must thereby be aware of the potential for thyroid-specific complications after ICM. We recommend a more thorough medical assessment of thyroid function before commencing any coronary intervention. The possibility of worsening thyroid dysfunction in patients with subclinical hyperthyroidism at baseline needs to be taken into account when administering high doses of iodide during PCI for coronary CTO lesions.

**Acknowledgements**

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**Statement of Ethics**

This study complies with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee.
Conflict of Interest

The authors declare no conflicts of interest.

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Author contributions

Çağın Mustafa ÜREYEN: Conception, Design, Data collection and/or processing, Analysis and/or interpretation, Literature review, Writer, Critical review of the study

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Sait Emir ŞAHİN: Conception, Data collection and/or processing, Literature review, Critical review of the study

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Harun KILIÇ: Design, Analysis and/or interpretation, Literature review, Critical review of the study

Mustafa Tarık AĞAÇ: Conception, Design, Analysis and/or interpretation, Literature review, Critical review of the study

Hüseyin GÜNDÜZ: Literature review, Writer, Critical review of the study

Ramazan AKDEMİR: Literature review, Writer, Critical review of the study

Ersan TATLI: Conception, Literature review, Writer, Critical review of the study
References


23. Eng PH, Cardona GR, Fang SL, Previti M, Alex S, Carrasco N, et al. Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid


Table 1: Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n: 205)</th>
<th>Group 2 (n:410)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>60.9±10.2</td>
<td>62.7±10.2</td>
<td>0.042</td>
</tr>
<tr>
<td>Male, n, %</td>
<td>173 (84.4)</td>
<td>320 (78)</td>
<td>0.063</td>
</tr>
<tr>
<td>Diabetes mellitus, n, %</td>
<td>83 (40.5)</td>
<td>163 (39.8)</td>
<td>0.861</td>
</tr>
<tr>
<td>Hypertension, n, %</td>
<td>101 (49.3)</td>
<td>191 (46.6)</td>
<td>0.530</td>
</tr>
<tr>
<td>Hyperlipidemia, n, %</td>
<td>106 (51.7)</td>
<td>200 (48.8)</td>
<td>0.494</td>
</tr>
<tr>
<td>Active smoking, n, %</td>
<td>68 (33.2)</td>
<td>140 (34.1)</td>
<td>0.809</td>
</tr>
<tr>
<td>Ex-smoker, n, %</td>
<td>77 (37.6)</td>
<td>144 (35.1)</td>
<td>0.552</td>
</tr>
<tr>
<td>History of MI</td>
<td>117 (57.1)</td>
<td>219 (53.4)</td>
<td>0.390</td>
</tr>
<tr>
<td>History of PCI</td>
<td>125 (61)</td>
<td>232 (56.6)</td>
<td>0.298</td>
</tr>
<tr>
<td>History of CVA</td>
<td>19 (9.3)</td>
<td>33 (8)</td>
<td>0.608</td>
</tr>
<tr>
<td>History of PAD</td>
<td>22 (10.7)</td>
<td>32 (7.8)</td>
<td>0.227</td>
</tr>
<tr>
<td>History of CHF</td>
<td>42 (20.5)</td>
<td>76 (18.5)</td>
<td>0.562</td>
</tr>
<tr>
<td>Baseline thyroid status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euthyroid</td>
<td>186 (90.8)</td>
<td>379 (92.4)</td>
<td></td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>14 (6.8)</td>
<td>25 (6.1)</td>
<td>0.642</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>5 (2.4)</td>
<td>6 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Median time of postprocedural thyroid function tests (day)*</td>
<td>147 (132-168)</td>
<td>152 (138-169)</td>
<td>0.197</td>
</tr>
<tr>
<td>Amount of ICM administered (ml)*</td>
<td>255 (195-300)</td>
<td>80 (65-90)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CHF: congestive heart failure, CVA: cerebrovascular accident, ICM: iodinated contrast medium, MI: myocardial infarction, PAD: peripheral arterial disease, PCI: percutaneous coronary intervention SD: standard deviation
*Data expressed in median and 25th and 75th percentiles in paranthesis
**Table 2:** The change in thyroid functions after percutaneous coronary interventions

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline euthyroid to subclinical</td>
<td>10 (5.4)</td>
<td>19 (5)</td>
<td>0.854</td>
</tr>
<tr>
<td>hyperthyroidism n, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline subclinical hyperthyroidism</td>
<td>7 (50)</td>
<td>3 (12)</td>
<td>0.019</td>
</tr>
<tr>
<td>to overt hyperthyroidism n, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline euthyroid to subclinical</td>
<td>0 (0)</td>
<td>2 (0.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>hypothyroidism n, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n: number of patients, %: percentage of patients
Figure Legends

Figure 1: The flowchart of patient enrollment; CTO: Chronic total occlusion, PCI: Percutaneous coronary intervention

Figure 2: The flowchart of change of thyroid functions in patients who underwent percutaneous coronary intervention of chronic total occlusion or non-complex coronary lesions; PCI: Percutaneous coronary intervention
A total of 208 patients who underwent PCI of CTO between July 2015 and December 2017 were assessed for eligibility.

3 patients who had been using thyroid replacement medication were excluded.

A total of 1550 patients who underwent non-complex PCI after July 2015 were assessed for eligibility.

1131 patients were excluded due to lack of postprocedural thyroid function tests.

419 patients who had a postprocedural thyroid function test 1–6 months after PCI.

7 patients who had been using thyroid replacement medication

+ 2 patients who had been using antithyroid medication

↓ excluded from the study

205 patients who underwent PCI CTO

+ 410 patients who underwent non-complex PCI

eligible for the study

Fig. 1
Fig. 2

205 Group I

615 Patients

205 Group II

Baseline

186 Euthyroid

5 Subclinical Hyperthyroidism

14 Subclinical Hyperthyroidism

379 Euthyroid

6 Subclinical Hypothyroidism

25 Subclinical Hyperthyroidism

After PCI

10 Subclinical Hyperthyroidism

176 Euthyroid

5 Subclinical Hypothyroidism

7 Subclinical Hyperthyroidism

7 Overt Hyperthyroidism

358 Euthyroid

19 Subclinical Hyperthyroidism

2 Subclinical Hypothyroidism

6 Subclinical Hyperthyroidism

22 Subclinical Hyperthyroidism

3 Overt Hyperthyroidism