ASSOCIATION BETWEEN IODINATED CONTRAST MEDIA EXPOSURE AND INCIDENT HYPERTHYROIDISM AND HYPOTHYROIDISM

Connie M. Rhee, MD; Ishir Bhan, MD, MPH; Erik K. Alexander, MD; Steven M. Brunelli, MD, MSCE

Background: Sudden exposure to high iodide levels may cause thyroid dysfunction. Despite compelling biological plausibility and clinical implication, the association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism has not been rigorously studied.

Methods: We performed a nested case-control study of patients treated between January 1, 1990, and June 30, 2010, who did not have preexisting hyperthyroidism or hypothyroidism. In parallel analyses, incident hyperthyroid or hypothyroid cases were defined by a change in thyrotropin level from normal (at baseline) to low or high (follow-up measurement). Euthyroid controls were selected using an incidence density sampling approach and were matched to cases on the basis of age, sex, race/ethnicity, estimated glomerular filtration rate, follow-up thyrotropin measurement date, and interval between baseline and the follow-up thyrotropin measurement date. Iodinated contrast media exposure was assessed using claims data for contrast-enhanced computed tomography or cardiac catheterization.

Results: In total, 178 and 213 incident hyperthyroid and hypothyroid cases, respectively, were matched to 655 and 779 euthyroid controls, respectively. Iodinated contrast media exposure was associated with incident hyperthyroidism (odds ratio [OR], 1.98; 95% CI, 1.08-3.60), but a statistically significant association with incident hypothyroidism was not observed (OR, 1.58; 95% CI, 0.95-2.62). In prespecified secondary analysis, iodinated contrast media exposure was associated with incident overt hyperthyroidism (follow-up thyrotropin level $\leq 0.1$ mIU/L; OR, 2.50; 95% CI, 1.06-5.93) and with incident overt hypothyroidism (follow-up thyrotropin level $> 10$ mIU/L; OR, 3.05; 95% CI, 1.07-8.72).

Conclusion: Iodinated contrast media exposure is associated with subsequent development of incident hyperthyroidism and incident overt hypothyroidism.

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IODINATED CONTRAST MEDIA (ICM) are commonly administered pharmaceutical agents. During the past 2 decades, their use has risen dramatically in parallel with 4- to 8-fold increases in cardiac catheterization and computed tomography.1 Although certain complications of ICM (eg, contrast-induced nephropathy) have been extensively studied, there has been little examination of the effect of ICM on thyroid function.1,2

Disorders of thyroid function have protean manifestations, including association with tachyarrhythmias,3-5 hypertensive crises,6 neuropyschiatric disturbances,7 and reproductive abnormalities.8 Hyperthyroidism and hypothyroidism increase the risk for coronary heart disease,6-8 left ventricular myopathy,6,8 electrophysiological abnormalities,7,9 and cardiovascular and all-cause mortality.10-14

A typical dose of ICM contains approximately 13 500 µg of free iodide15 and 15 to 60 g of bound iodine1 that may be liberated as free iodide in the body.15-16 This represents an acute iodide load of 90 to several hundred thousand times the recommended daily intake of 150 µg.17 Sudden exposure to high iodide loads, given in other contexts, can disrupt thyroid hormone regulation, resulting in hypothyroidism (Wolff-Chaikoff effect)18,19 or hyperthyroidism (jodbasedow).18,20

Despite ubiquitous use of ICM, a compelling biologically plausible association, and increasing recognition of hyperthyroidism and hypothyroidism sequelae, there have been few studies of the association between ICM exposure and subsequent thyroid functional derangements. Prior studies provide limited evidence owing to small
sample size, lack of distinction between hyperthyroidism and hypothyroidism, short-term follow-up, and, most notably, the absence of unexposed control groups against whom risk could be compared. To address these limitations, we conducted a nested case-control study to assess the association between ICM exposure and incident thyroid dysfunction.

METHODS

STUDY COHORT

The study protocol was approved by the Partners HealthCare Institutional Review Board, Boston, Massachusetts. We performed a nested case-control study using data from the Partners HealthCare Research Patient Data Registry, which aggregates data on sociodemographics, diagnostic codes, procedural claims, laboratory results, medication use, inpatient and ambulatory encounters, and vital status for more than 4.5 million patients receiving care at Brigham and Women’s Hospital and at Massachusetts General Hospital. This database is updated quarterly, provides the ability to follow up patients longitudinally, and has been used in numerous epidemiological studies.

The source cohort consisted of adult patients who met the following criteria: (1) a normal thyrotropin level between January 1, 1990, and June 30, 2010 (baseline); (2) no prior laboratory evidence of abnormal thyroid function (thyrotropin, free thyroxine, free thyroxine index, or total thyroxine level outside the normal range); (3) no prior diagnosis of hypothyroidism or hyperthyroidism; (4) no past or concurrent use of thyroid hormone supplementation or thyroid suppressive medication; (5) no radioactive iodine ablation or surgical thyroidectomy; and (6) a subsequent thyrotropin measurement within 2 weeks to 2 years (follow-up measurement) (Figure 1). Criteria 1 through 5 were to ensure that we were considering incident thyroid functional disease. Criterion 6 was to ensure opportunity for possible intervening ICM exposure (≥2 weeks) and to ensure sufficient continuity of care within the Partners HealthCare system during which ICM exposure could be reliably captured (≤2 years). Patients were eligible to contribute 1 or more intervals to the analyses, provided that each interval met the aforementioned criteria; intervals could be consecutive or nonconsecutive.

CASES, CONTROLS, AND ICM EXPOSURE

Because thyroid function was normal at the start of each patient interval, case status was determined by follow-up thyrotropin level: incident hyperthyroidism was defined as a thyrotropin level below the assay reference range, incident hypothyroidism was defined as a thyrotropin level above the assay reference range, and control thyrotropin level was defined as within the assay reference range. The total thyroxine level, free thyroxine level, and free thyroxine index were measured almost exclusively in response to abnormal thyrotropin levels; therefore, they could not be included in the primary case definition because there would have been no control group. In secondary analysis, we considered incident overt hyperthyroidism (follow-up thyrotropin level ≥0.1 mIU/L) and incident overt hypothyroidism (follow-up thyrotropin level >10 mIU/L) based on evidence that such levels are associated with cardiovascular morbidity and mortality and are less likely to be due to nonthyroidal illness.

Parallel analogous analyses were conducted for incident hyperthyroidism, incident overt hyperthyroidism, incident hypothyroidism, and incident overt hypothyroidism. As is the preferred means of analysis for case-control studies, controls were sampled using an incidence density sampling approach. Thereby, at each historical time point at which a case was identified, we randomly selected up to 4 controls (having concurrent intervals ending with a normal follow-up thyrotropin level). Aside from providing for better estimation, this approach advantageously accounts for secular trends in ICM use and thyrotropin assay drift and defines a period over which to consider ICM exposure among controls. Controls were eligible to be matched to more than 1 case.
INCIDENT HYPERTHYROIDISM

To minimize confounding, controls were matched to cases on the basis of the following: sex, age (within 10 years), race/ethnicity (white vs nonwhite), follow-up thyrotropin measurement date (within 2 years), interval between baseline and the follow-up thyrotropin measurement date (\(\leq 180\) vs. \(181-360\), \(361-540\), or \(541-720\) days), and estimated glomerular filtration rate (derived from the modified 4-variable Modification of Diet in Renal Disease Study equation\(^{35}\) using the most proximate creatinine level within 1 year preceding the baseline thyrotropin measurement date (\(\leq 45\), 46-60, or \(>60\) mL/min/1.73 m\(^2\) or missing)).

For each patient interval (cases and controls), ICM exposure was defined as baseline and the follow-up thyrotropin measurement date. Iodinated contrast media exposure was derived from procedural claims for contrast-enhanced computed tomography or for cardiac catheterization using ICM.

STATISTICAL ANALYSIS

Within each group (control, hyperthyroid, or hypothyroid), change in thyrotropin level from baseline to follow-up measurement was assessed using Wilcoxon signed rank test. Comparisons of baseline characteristics between cases and matched controls were performed using linear regression analysis (with variance estimates clustered on matched group assignment) and conditional logistic regression analysis for continuous and categorical variables, respectively. The association between ICM exposure and outcome was estimated using conditional logistic regression models grouped on matched assignment. Effect modification of the association between ICM exposure and outcome was estimated by comparing nested models with and without a 2-way factor by ICM exposure cross-product term using likelihood ratio testing. The number needed to harm was calculated as follows: \[1/([\text{Odds Ratio} − 1] \times [\text{Risk Among Unexposed}])\].\(^{36}\) Analyses were performed using commercially available software (STATA, version 10.1; StataCorp LP).

RESULTS

SOURCE COHORT DESCRIPTION

The source cohort consisted of 4096 patient intervals, among which 191 incident hyperthyroid cases and 227 incident hypothyroid cases were identified; 3678 patient intervals served as eligible controls. As expected, thyrotropin levels did not change between baseline and follow-up measurement among controls, fell among incident hyperthyroid cases, and rose among incident hypothyroid cases (Figure 2). Iodinated contrast media was administered in 361 patient intervals (8.8%); the context and timing of administration are summarized in Table 1.

To assess case definition validity, we examined the proportion of cases with corroborative evidence of hyperthyroidism or hypothyroidism on or after follow-up thyrotropin measurement (Table 2). Among incident hyperthyroid and hypothyroid cases, 101 (52.9%) and 151 (66.5%) had corroborative evidence, respectively (confirmed cases). No patient had discordant evidence (eg, low thyroxine level among patients with low thyrotropin level) that was suggestive of secondary disease.

ASSOCIATION BETWEEN ICM EXPOSURE AND INCIDENT HYPERTHYROIDISM

Among 191 incident hyperthyroid cases, 178 (93.2%) were matched to 655 controls. Incident hyperthyroid cases and matched controls were balanced on baseline covariates (Table 3). In matched analysis, there was a potent association between ICM exposure and incident hyperthyroidism (odds ratio [OR], 1.98; 95% CI, 1.08-3.60; \(P = .03\)) (Figure 3). The number needed to harm was 23. There was no observed effect modification on the basis of sex, race/ethnicity, renal function, or interval between base-
line and follow-up thyrotropin measurement (Table 4). Results were similar in sensitivity analysis limited to 95 confirmed cases and 358 matched controls (OR, 2.26; 95% CI, 1.07-4.76).

In prespecified secondary analysis, we examined the association between ICM exposure and incident overt hyperthyroidism in 82 cases, of whom 76 were matched to 285 controls (OR, 2.50; 95% CI, 1.06-5.93; \( P = .04 \)) (Figure 3). Compared with the remaining hyperthyroidism cases, patients developing incident overt hyperthyroidism were more likely to be female (85.4% vs 72.5%, \( P = .03 \)) but were similar in age (mean [SD], 48.0 [1.6] vs 46.2 [1.5] years; \( P = .42 \)), prevalence of renal dysfunction (7.3% vs 7.3%, \( P = .97 \)), and nonwhite race/ethnicity (26.8% vs 28.4%, \( P = .81 \)).

### ASSOCIATION BETWEEN ICM EXPOSURE AND INCIDENT HYPOTHYROIDISM

Among 227 incident hypothyroid cases, 213 (93.8%) were matched to 779 controls. Incident hypothyroid cases and matched controls were balanced on all baseline covariates (Table 3). In matched analysis, no statistically significant association between ICM exposure and incident hypothyroidism was observed (OR, 1.58; 95% CI, 0.95-2.62; \( P = .08 \)) (Figure 3). The number needed to harm was 33. There was

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#### Table 2. Corroborative Events Following Designation of an Incident Hyperthyroid Case or Hypothyroid Case by Thyrotropin Measurement Criteria

<table>
<thead>
<tr>
<th>Event</th>
<th>Incident Hyperthyroid Cases (n=191)</th>
<th>Incident Hypothyroid Cases (n=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Time to Event, Median, d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corresponding diagnosis(^a)</td>
<td>72 (37.7)</td>
<td>116</td>
</tr>
<tr>
<td>Medication initiation(^b)</td>
<td>16 (8.4)</td>
<td>13</td>
</tr>
<tr>
<td>Corresponding changes in total thyroxine level, free thyroxine level, and free thyroxine index(^c)</td>
<td>66 (34.6)</td>
<td>2</td>
</tr>
<tr>
<td>Radioactive iodine or surgical thyroid ablation</td>
<td>21 (11.0)</td>
<td>517</td>
</tr>
<tr>
<td>Any of the above</td>
<td>101 (52.9)</td>
<td>35</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

\(^a\) International Classification of Diseases, Ninth Revision, code diagnosis of hyperthyroidism for incident hyperthyroid cases and diagnosis of hypothyroidism for incident hypothyroid cases.

\(^b\) Thyroid suppressive medication for incident hyperthyroid cases and thyroid hormone supplementation for incident hypothyroid cases.

\(^c\) Above the upper limit of the reference range for incident hyperthyroid cases and below the lower limit of the reference range for incident hypothyroid cases.

#### Table 3. Comparison of Baseline Characteristics Between Incident Hyperthyroid and Hypothyroid Cases vs Matched Controls\(^a\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Matched Controls (n=655)</th>
<th>Incident Hyperthyroid Cases (n=178)</th>
<th>( P ) Value</th>
<th>Matched Controls (n=779)</th>
<th>Incident Hypothyroid Cases (n=213)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>46.5 (14.2)</td>
<td>46.5 (14.8)</td>
<td>&gt;.99</td>
<td>51.3 (16.8)</td>
<td>51.9 (17.8)</td>
<td>.12</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>543 (82.9)</td>
<td>145 (81.5)</td>
<td>NA</td>
<td>586 (75.2)</td>
<td>157 (73.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Nonwhite race/ethnicity, No. (%)</td>
<td>143 (21.8)</td>
<td>45 (25.5)</td>
<td>NA</td>
<td>77 (9.9)</td>
<td>26 (12.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min/1.73 m(^2), No. (%)(^c)</td>
<td>440 (67.2)</td>
<td>113 (63.5)</td>
<td>NA</td>
<td>512 (65.7)</td>
<td>134 (62.9)</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;60</td>
<td>18 (2.7)</td>
<td>9 (5.1)</td>
<td>NA</td>
<td>98 (12.6)</td>
<td>31 (14.6)</td>
<td>NA</td>
</tr>
<tr>
<td>(\leq) 60</td>
<td>197 (30.1)</td>
<td>56 (31.5)</td>
<td>NA</td>
<td>169 (21.7)</td>
<td>48 (22.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Interval between baseline and the follow-up thyrotropin measurement date, median (25th-75th percentiles), d</td>
<td>252 (122-403)</td>
<td>263 (100-406)</td>
<td>.13</td>
<td>272 (132-418)</td>
<td>280 (139-401)</td>
<td>.81</td>
</tr>
<tr>
<td>Study era, No. (%)</td>
<td>1990-1995</td>
<td>89 (13.6)</td>
<td>30 (16.9)</td>
<td>.99</td>
<td>89 (11.4)</td>
<td>27 (12.7)</td>
</tr>
<tr>
<td>1996-2000</td>
<td>147 (22.4)</td>
<td>38 (21.3)</td>
<td>.74</td>
<td>158 (20.0)</td>
<td>45 (21.1)</td>
<td>.93</td>
</tr>
<tr>
<td>2001-2005</td>
<td>256 (39.1)</td>
<td>69 (38.8)</td>
<td>.32</td>
<td>306 (39.3)</td>
<td>83 (39.0)</td>
<td>.83</td>
</tr>
<tr>
<td>2006-2010</td>
<td>163 (24.9)</td>
<td>41 (23.0)</td>
<td>.32</td>
<td>228 (29.3)</td>
<td>58 (27.2)</td>
<td>.83</td>
</tr>
<tr>
<td>Iodinated contrast media exposure, No. (%)</td>
<td>40 (6.1)</td>
<td>19 (10.7)</td>
<td>.25</td>
<td>66 (8.5)</td>
<td>26 (12.2)</td>
<td>.25</td>
</tr>
</tbody>
</table>

Abbreviation: NA, no \( P \) value could be calculated owing to no difference within matched groups.

\(a\) \( P \) values for continuous variables are derived from a linear regression model with variance clustered on matched group assignment. \( P \) values for era are derived from a conditional logistic regression model grouped on matched assignment.

\(b\) In total, 152, 5, 11, and 10 incident hyperthyroid cases were matched to 4, 3, 2, and 1 controls, respectively. In total, 181, 6, 11, and 15 incident hypothyroid cases were matched to 4, 3, 2, and 1 controls, respectively.

\(c\) Matched in categories of 45 or less, 46 to 60, or greater than 60 mL/min/1.73 m\(^2\) or missing. The 45 or less and 46 to 60 mL/min/1.73 m\(^2\) categories have been collapsed here owing to sparsity.
The observed association between ICM exposure and incident hyperthyroidism is likely explained by the iodine load conveyed by ICM. Under physiological conditions, the capture and organification of iodide and the subsequent synthesis and release of triiodothyronine and thyroxine are tightly regulated. However, exposure to supraphysiological levels of iodide may overwhelm regulatory capacity and precipitate hyperthyroidism via iodine-induced thyrotoxicosis. This effect has been seen with a daily iodine dose of 300 to 500 mg in patients with iodide deficiency and increased thyroid function. However, unless definitive evidence suggests a role, such as a large-scale study with statistical power, we cannot definitively assess whether thyroid autoantibodies modified the observed association between ICM exposure and incident hyperthyroidism owing to scant titer measurement among controls. The high positivity rates among cases in whom titers were measured may suggest a possible mediating role. However, such interpretation must be tempered by realization that titers were measured in 44 of 191 incident hyperthyroid cases, 22 of 227 incident hypothyroid cases, and 537 matched controls (OR, 1.56; 95% CI, 0.86-2.82).

INTERPLAY OF AUTOIMMUNE THYROID FUNCTIONAL DISEASE

To our knowledge, this represents the first large controlled study of the association between ICM exposure and incident thyroid functional disease. We observed significant association between ICM exposure and incident hyperthyroidism, incident overt hyperthyroidism, and incident hyperthyroidism and incident overt hypothyroidism. Each was estimated in separate parallel analyses, controlling by matching for age, sex, race/ethnicity, estimated glomerular filtration rate, follow-up thyrotropin measurement date, and interval between baseline and the follow-up thyrotropin measurement date.
isom (if externally validated) is of considerable clinical importance given the effects of prolonged hyperthyroid status on cardiovascular disease and survival.5-10,12,14,46

Iodide excess can also lead to hypothyroidism through impairments in sodium iodide transport, iodine organification, and thyroid hormone synthesis and secretion via Wolff-Chaikoff effect. We observed no association between ICM exposure and incident hypothyroidism overall. Possible explanations include a type II error, the absence of a biological effect, or concealment of a transient effect owing to the prolonged interval between ICM exposure and follow-up thyrotropin measurement. Following Wolff-Chaikoff effect, patients often regain normal thyroid function over weeks to months due to reductions in sodium iodide transporter expression and activity and restoration of normal intrathyroidal iodine concentrations.18,57-49 This may account for the potent association between ICM exposure and incident hypothyroidism observed when the interval between baseline and follow-up thyrotropin measurement was short but not long. It is unknown whether the association between ICM exposure and incident overt hypothyroidism observed was due to chance, failed escape from Wolff-Chaikoff effect,18 or an improved ratio of signal to noise (ie, less variance resulting from false-positive results).

Strengths of our study include rigorous inclusion and exclusion criteria used to restrict consideration to incident thyroid disease. In addition, we controlled for potential confounding by matching on the basis of age, sex, race/ethnicity, renal function, study era, and interval between baseline and follow-up thyrotropin measurement. Despite the number of variables, matching efficiency was high. However, as with all observational studies, we cannot exclude the possibility of residual confounding.

Several limitations of our study bear mention. First, patients were required to have successive thyrotropin measurements within 2 years, which was essential to ensure that consideration was limited to incident disease. Although we could not ascertain indications for frequent thyrotropin measurement, we speculate that patients may have had a higher-than-average perceived risk of developing thyroid functional disorders. That criteria were applied equally to cases and controls precludes threat to internal validity (ie, bias) but may limit generalizability, particularly with respect to estimates for numbers needed to harm. Second, there were limited available data on total thyroxine level, free thyroxine level, and free thyroxine index. Case definitions relied solely on thyrotropin levels, which are subject to misclassification (eg, among patients with euthyroid sick syndrome). However, in all instances when corroborative data were available, these were concordant with case assignment based on thyrotropin level; any resultant misclassification would have been nondifferential and biased findings toward the null. Moreover, that observed associations were equally to more potent in sensitivity analyses limited to cases with confirmatory evidence of thyroid functional disease, as well as those in which case definition was based on more restrictive thyrotropin thresholds, is further evidence that results were not overly biased by patients with euthyroid sick syndrome. Third, we lacked data on ICM exposure and thyroid functional tests performed outside of the Partners HealthCare system. Again, resultant misclassification is expected to be nondifferential, rendering estimates conservative. Fourth, we lacked data on contrast volume and osmolarity. However, given the degree to which ICM iodine content exceeds physiological levels, a several-fold difference in iodine quantity conferred by volume and osmolarity is unlikely to be further meaningful with respect to thyroid function.

In summary, these data support association between ICM exposure and incident hyperthyroidism, incident overt hyperthyroidism, and incident overt hypothyroidism. Given the pervasive use of ICM in contemporary practice and the known sequelae of thyroid functional derangements, further studies are needed to confirm and evaluate generalizability of these findings, to establish causality, and to explore mechanisms. Physicians and patients should be aware of the potential thyroidal complications associated with ICM procedures and should use appropriate discretion in their use.

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Correspondence: Steven M. Brunelli, MD, MSCE, Renal Division, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, 75 Francis St, Ste MRB-4, Boston, MA 02115 (sbrunelli@partners.org).

Author Contributions: Dr Brunelli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rhee, Bhan, and Brunelli.

Acquisition of data: Rhee and Brunelli.

Analysis and interpretation of data: Rhee, Bhan, Alexander, and Brunelli.

Drafting of the manuscript: Rhee, Alexander, and Brunelli.

Critical revision of the manuscript for important intellectual content: Rhee, Bhan, Alexander, and Brunelli.

Statistical analysis: Rhee and Brunelli.

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Additional Contributions: Partners HealthCare Research Patient Data Registry Group provided access to the data used in these analyses.

REFERENCES

Iodine-Induced Thyroid Dysfunction

Evaluating the Risks of Iodinated Contrast Medium

In this issue of the Archives, Rhee et al report the findings of a nested case-control study examining associations between exposure to iodinated radiologic contrast media and development of incident thyroid dysfunction. They describe significant associations between contrast exposure and the development of hyperthyroidism. While no overall association exists between contrast exposure and all forms of hypothyroidism, an association was noted when cases were restricted to those with overt hypothyroidism. There was also an...