

LESS IS MORE

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 ≤ 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.

Arch Intern Med. 2012;172(2):153-159

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}

See Invited Commentary and Editor's Note at end of article

Disorders of thyroid function have protean manifestations, including association with tachyarrhythmias,³⁻⁵ hypertensive crises,³ neuropsychiatric disturbances,³ and reproductive abnormalities.⁴ 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 iodine¹⁵ 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

Author Affiliations: Renal Division (Drs Rhee and Brunelli), Endocrinology, Diabetes, and Hypertension Division (Dr Alexander), and Pharmacoepidemiology Division (Dr Brunelli), Department of Medicine, Brigham and Women's Hospital, and Renal Division, Department of Medicine, Massachusetts General Hospital (Dr Bhan), Harvard Medical School, Boston.

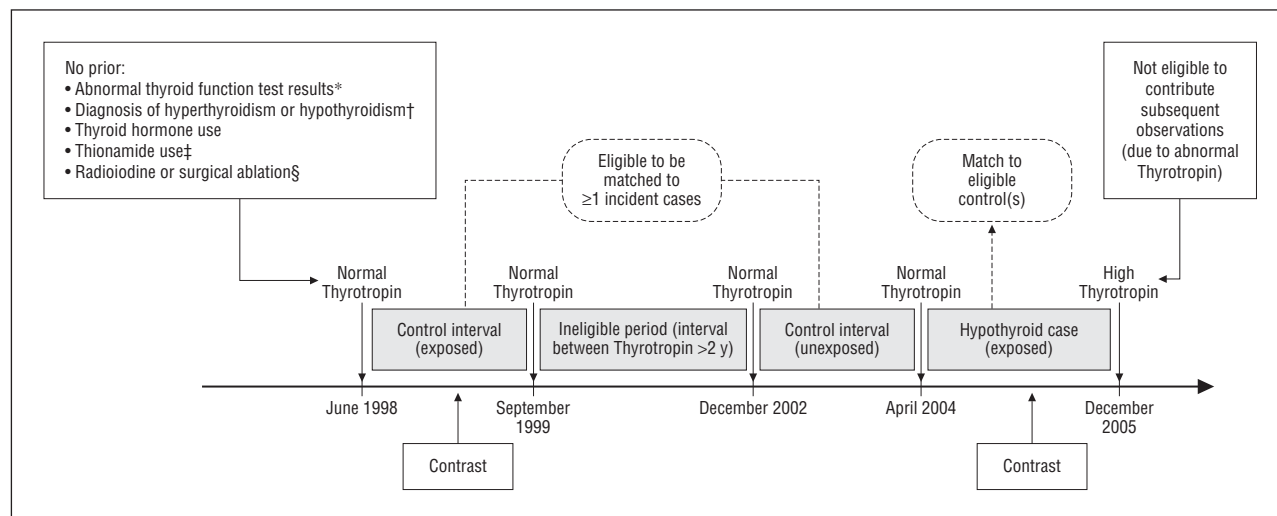


Figure 1. Example of the operational definitions of eligibility, iodinated contrast media exposure, and case definition based on a hypothetical patient's longitudinal experience. This patient is eligible to contribute 2 control intervals (normal baseline and follow-up thyrotropin measurement from June 1998 to September 1999 and from December 2002 to April 2004). In addition, the patient contributes a case interval to the hypothyroidism analysis (normal baseline and high follow-up thyrotropin measurement from April 2004 to December 2005). Following the elevated thyrotropin measurement in December 2005, the patient can no longer contribute eligible intervals for analysis. One intervening interval was not eligible for analysis because the follow-up thyrotropin level (December 2002) was measured more than 2 years after the baseline thyrotropin level (September 1999). *Abnormal thyroid function test results include thyrotropin level, free thyroxine level, free thyroxine index, and total thyroxine level. †Diagnosis of hyperthyroidism or hypothyroidism based on *International Classification of Diseases, Ninth Revision (ICD-9)*, codes 242.xx, 244.xx, 245.xx, 648.1x, and 794.5. ‡Thionamides: methimazole and propylthiouracil. §Radioactive iodine and surgical ablation based on *ICD-9* codes 06.4 and 06.52 and *Current Procedural Terminology* codes 60240, 60252, 60254, 60260, 60270, 60271, 79000, 79001, 79030, and 79035.

sample size,²¹⁻²⁵ failure to restrict consideration to incident thyroid disease,^{24,25} lack of distinction between hyperthyroidism and hypothyroidism,²⁵ short-term follow-up,^{22,23,25} and, most notably, the absence of unexposed control groups against whom risk could be compared.²¹⁻²⁶ 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.²⁷⁻²⁹

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 in-

tervening 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.^{9,13,30-32}

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,^{33,34} 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.^{33,34}

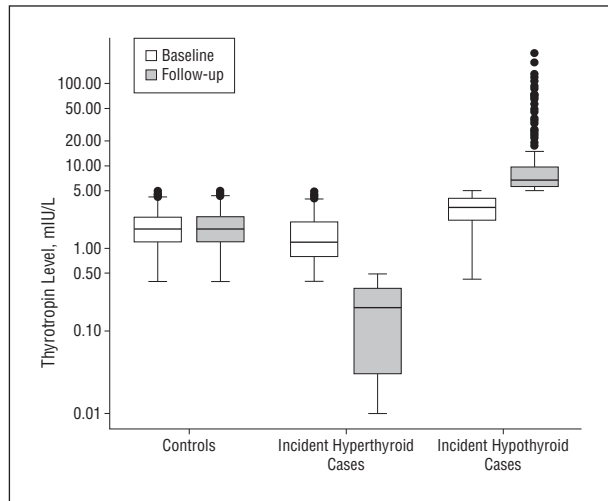


Figure 2. Baseline and follow-up thyrotropin levels among eligible controls, incident hyperthyroid cases, and incident hypothyroid cases (irrespective of iodinated contrast media exposure status). The boxes span the 25th to 75th percentiles, the internal line indicates the median, whiskers extend to the upper and lower adjacent values, and dots indicate statistical outliers. Among eligible controls, the median (interquartile [IQR]) baseline, follow-up, and delta thyrotropin levels were 1.71 (1.18-2.39), 1.72 (1.19 to 2.43), and 0.01 (-0.40 to 0.45) mIU/L, respectively ($P=.14$, Wilcoxon signed rank test for baseline to follow-up). Among incident hyperthyroid cases, the median (IQR) baseline, follow-up, and delta thyrotropin levels were 1.19 (0.80 to 2.08), 0.19 (0.03 to 0.33), and -1.05 (-2.02 to -0.54) mIU/L, respectively ($P<.001$, Wilcoxon signed rank test for baseline to follow-up). Among incident hypothyroid cases, the median (IQR) baseline, follow-up, and delta thyrotropin levels were 3.14 (2.20 to 4.03), 6.72 (5.56 to 9.70), and 3.82 (2.20 to 7.50) mIU/L, respectively ($P<.001$, Wilcoxon signed rank test for baseline to follow-up). The assay upper or lower limit of detection was used as a proxy when results were reported as less than the lower limit or greater than the upper limit of detection; the y-axis is plotted on a log scale.

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 (≤ 180 , 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 equation³⁵ using the most proximate creatinine level within 1 year preceding the baseline thyrotropin measurement date [≤ 45 , 46-60, or > 60 mL/min/1.73 m² or missing]).

For each patient interval (cases and controls), ICM exposure was defined as between 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 ra-

Table 1. Context and Timing of Administration of ICM Among 4096 Patient Intervals

Variable	Value
Context of ICM exposure, No. (%) of patient intervals	
Any cardiac catheterization or computed tomography	361 (8.8)
Computed tomography alone	292 (7.1)
Cardiac catheterization alone	49 (1.2)
Both cardiac catheterization and computed tomography	20 (0.5)
Interval between ICM exposure and the follow-up thyrotropin measurement date	
Median (interquartile range), d	158 (50-294)
No. (%) of 361 patient intervals	
≤ 4 wk	72 (19.9)
≤ 2 wk	53 (14.7)
≤ 1 wk	43 (11.9)

Abbreviation: ICM, iodinated contrast media.

tio 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-

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

Event	Incident Hyperthyroid Cases (n=191)		Incident Hypothyroid Cases (n=227)	
	No. (%)	Time to Event, Median, d	No. (%)	Time to Event, Median, d
Corresponding diagnosis ^a	72 (37.7)	116	136 (59.9)	356
Medication initiation ^b	16 (8.4)	13	118 (52.0)	529
Corresponding changes in total thyroxine level, free thyroxine level, and free thyroxine index ^c	66 (34.6)	2	65 (28.6)	7
Radioactive iodine or surgical thyroid ablation	21 (11.0)	517	NA	NA
Any of the above	101 (52.9)	35	151 (66.5)	71

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

Characteristic	Matched Controls (n=655)	Incident Hyperthyroid Cases (n=178) ^b	P Value	Matched Controls (n=779)	Incident Hypothyroid Cases (n=213) ^b	P Value
Age, mean (SD), y	46.5 (14.2)	46.5 (14.8)	>.99	51.3 (16.8)	51.9 (17.8)	.12
Female sex, No. (%)	543 (82.9)	145 (81.5)	NA	586 (75.2)	157 (73.7)	NA
Nonwhite race/ethnicity, No. (%)	143 (21.8)	45 (25.3)	NA	77 (9.9)	26 (12.2)	NA
Estimated glomerular filtration rate, mL·min ⁻¹ ·1.73 m ² , No. (%) ^c						
>60	440 (67.2)	113 (63.5)	NA	512 (65.7)	134 (62.9)	NA
≤60	18 (2.7)	9 (5.1)		98 (12.6)	31 (14.6)	
Missing	197 (30.1)	56 (31.5)		169 (21.7)	48 (22.5)	
Interval between baseline and the follow-up thyrotropin measurement date, median (25th-75th percentiles), d	252 (122-403)	263 (100-406)	.13	272 (132-418)	280 (133-401)	.81
Study era, No. (%)						
1990-1995	89 (13.6)	30 (16.9)	.74	89 (11.4)	27 (12.7)	.93
1996-2000	147 (22.4)	38 (21.3)		156 (20.0)	45 (21.1)	
2001-2005	256 (39.1)	69 (38.8)		306 (39.3)	83 (39.0)	
2006-2010	163 (24.9)	41 (23.0)		228 (29.3)	58 (27.2)	
Iodinated contrast media exposure, No. (%)	40 (6.1)	19 (10.7)		66 (8.5)	26 (12.2)	

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 m² or missing. The 45 or less and 46 to 60 mL/min/1.73 m² categories have been collapsed here owing to sparsity.

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 hyperthyroid 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

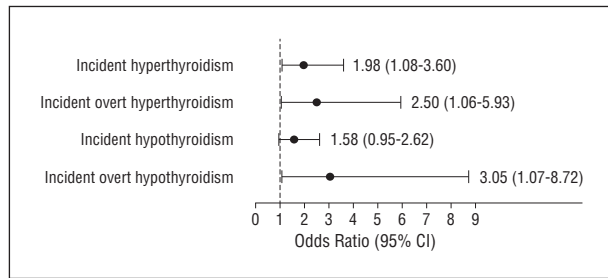


Figure 3. Overall association between iodinated contrast media exposure and incident hyperthyroidism, incident overt hyperthyroidism, incident hypothyroidism, and incident overt hypothyroidism. Each was estimated in separate parallel analyses, controlling by matching for age, sex, race/ethnicity, estimated glomerular filtration rate, follow-up thyrotropin measurement date, and interval between baseline and the follow-up thyrotropin measurement date.

effect modification on the basis of the interval between baseline and follow-up thyrotropin measurement such that ICM was potentially associated with incident hypothyroidism during intervals of 180 days or less but not greater than 180 days (Table 4). The association between ICM exposure and hypothyroidism was not modified by sex, race/ethnicity, or renal function. Results were similar in sensitivity analysis limited to 143 confirmed cases and 537 matched controls (OR, 1.56; 95% CI, 0.86-2.82).

In prespecified secondary analysis, we examined the association between ICM exposure and incident overt hypothyroidism in 56 cases, of whom 52 were matched to 188 controls (OR, 3.05; 95% CI, 1.07-8.72; $P = .04$) (Figure 3). Compared with the remaining hypothyroid cases, patients developing incident overt hypothyroidism were less likely to have renal dysfunction (7.1% vs 18.7%, $P = .003$) but were similar in age (mean [SD], 49.5 [2.2] vs 52.7 [1.4] years, $P = .25$), female sex (78.6% vs 69.6%, $P = .21$), and nonwhite race/ethnicity (16.1% vs 12.9%, $P = .54$).

ANTITHYROID ANTIBODIES

Antithyroid peroxidase antibody or antithyroglobulin titers were measured in 44 of 191 incident hyperthyroid cases (23.0%) and in 54 of 227 incident hypothyroid cases (23.8%). Data on thyrotropin antibody titers were unavailable. Titers were positive in 21 incident hyperthyroid cases (47.7% of those tested); similar proportions of those with positive and negative titers had ICM exposure (4 of 21 vs 3 of 23; $P = .45$, Fisher exact test). Titers were positive in 22 incident hypothyroid cases (40.7% of those tested); similar proportions of those with positive and negative titers had ICM exposure (1 of 22 vs 2 of 32; $P = .64$, Fisher exact test).

COMMENT

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 overt hypothyroidism but not incident hypothyroidism overall.

Table 4. Analysis of Effect Modification of the Association Between Iodinated Contrast Media Exposure and Incident Hyperthyroidism and Hypothyroidism^a

Variable	P Value for Interaction
Incident hyperthyroidism	
Baseline renal function	.63
Sex	.99
Race/ethnicity	.53
Interval between baseline and the follow-up thyrotropin measurement date	.77
Incident hypothyroidism	
Baseline renal function	.39
Sex	.16
Race/ethnicity	.56
Interval between baseline and the follow-up thyrotropin measurement date ^b	.02

^aBaseline renal function is an estimated glomerular filtration rate of 60 or less vs greater than 60 mL/min/1.73 m². Race/ethnicity is white vs nonwhite. Interval between baseline and the follow-up thyrotropin measurement date is 180 or less vs greater than 180 days.

^bStratum-specific odds ratios (95% CIs) are 3.34 (1.48-7.54) for 180 days or less and 0.94 (0.47-1.91) for greater than 180 days.

The observed association between ICM exposure and incident hyperthyroidism is likely explained by the iodine or iodide 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.^{37,38} However, exposure to supraphysiological levels of iodide may overwhelm regulatory capacity and precipitate hyperthyroidism via jodbasedow.^{15,18,39} This effect has been seen with 300 to 500 µg of iodide,¹⁸ which is much less than that conveyed by ICM. Jodbasedow is classically described among patients with autoimmune thyroid disease in whom iodine deficiency masks the expression of hyperthyroidism, patients with autonomous nodular goiters,^{20,40-42} and older populations (among whom the prevalence of nodular disease is high).⁴³ Although controversial, iodine-induced thyrotoxicosis has been reported in patients without underlying thyroid disease.^{18,39,40,44,45} We could not 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 only a small (possibly selected) subset of cases, ICM exposure was similar among autoantibody-positive and autoantibody-negative cases, and the source population was drawn from an iodine-replete region. We cannot exclude the possibility that incident hyperthyroid cases had underlying multinodular goiters, as clinical recognition and administrative data capture of such lesions are poor. Nonetheless, these data leave open the possibility that iodine-induced hyperthyroidism among patients without predisposing lesions is more commonplace than previously recognized. Dedicated mechanistic studies are needed. Regardless of mechanism, the observed association between ICM exposure and incident hyperthyroid-

ism (if externally validated) is of considerable clinical importance given the effects of prolonged hyperthyroid status on cardiovascular disease and survival.^{6-10,12,14,46}

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 restitution of normal intrathyroidal iodine concentrations.^{18,47-49} 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 ex-

posure 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 osmolality. However, given the degree to which ICM iodine content exceeds physiological levels, a several-fold difference in iodine quantity conferred by volume and osmolality 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.

Accepted for Publication: September 11, 2011.

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. *Obtained funding:* Rhee and Brunelli. *Administrative, technical, or material support:* Rhee and Brunelli. *Study supervision:* Brunelli.

Financial Disclosure: Dr Alexander receives research support from Veracyte, Inc, and Asuragen, Inc.

Funding/Support: This work was supported by grants DK007527-26 (Dr Rhee) and DK079056 (Dr Brunelli) from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Role of the Sponsors: The National Institutes of Health had no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

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

REFERENCES

1. Katzberg RW, Haller C. Contrast-induced nephrotoxicity: clinical landscape. *Kidney Int Suppl.* 2006;(100):S3-S7.
2. Mudge GH. Nephrotoxicity of urographic radiocontrast drugs. *Kidney Int.* 1980; 18(5):540-552.
3. Arit S, Burkhardt D, Wiedemann K. Thyrotoxicosis after iodine contrast medium administration: rapid mood swing to mania and subsequent psychotic depression in a patient with bipolar disorder during lithium therapy. *Pharmacopsychiatry.* 2008;41(4):163-165.
4. Müssig K, Thamer C, Bares R, Lipp HP, Häring HU, Gallwitz B. Iodine-induced

- thyrotoxicosis after ingestion of kelp-containing tea. *J Gen Intern Med.* 2006;21(6):C11-C14.
5. Robertson P, Fraser J, Sheild J, Weir P. Thyrotoxicosis related to iodine toxicity in a paediatric burn patient. *Intensive Care Med.* 2002;28(9):1369.
 6. Gerdes AM, Iervasi G. Thyroid replacement therapy and heart failure. *Circulation.* 2010;122(4):385-393.
 7. Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. *Endocr Rev.* 2005;26(5):704-728.
 8. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med.* 2001;344(7):501-509.
 9. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med.* 1994;331(19):1249-1252.
 10. Haentjens P, Van Meerhaeghe A, Poppe K, Velkeniers B. Subclinical thyroid dysfunction and mortality: an estimate of relative and absolute excess all-cause mortality based on time-to-event data from cohort studies. *Eur J Endocrinol.* 2008;159(3):329-341.
 11. Imaizumi M, Akahoshi M, Ichimaru S, et al. Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2004;89(7):3365-3370.
 12. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet.* 2001;358(9285):861-865.
 13. Rodondi N, den Elzen WP, Bauer DC, et al; Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA.* 2010;304(12):1365-1374.
 14. Sgarbi JA, Matsumura LK, Kasamatsu TS, Ferreira SR, Maciel RM. Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese-Brazilian thyroid study. *Eur J Endocrinol.* 2010;162(3):569-577.
 15. van der Molen AJ, Thomsen HS, Morcos SK; Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). Effect of iodinated contrast media on thyroid function in adults. *Eur Radiol.* 2004;14(5):902-907.
 16. Moisey RS, McPherson S, Wright M, Orme SM. Thyroiditis and iodine mumps following an angioplasty. *Nephrol Dial Transplant.* 2007;22(4):1250-1252.
 17. Trumbo P, Yates AA, Schlicker S, Poos M. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. *J Am Diet Assoc.* 2001;101(3):294-301.
 18. Bürgi H. Iodine excess. *Best Pract Res Clin Endocrinol Metab.* 2010;24(1):107-115.
 19. Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. *J Biol Chem.* 1948;174(2):555-564.
 20. Martins MC, Lima N, Knobel M, Medeiros-Neto G. Natural course of iodine-induced thyrotoxicosis (jodbasedow) in endemic goiter area: a 5 year follow-up. *J Endocrinol Invest.* 1989;12(4):239-244.
 21. Breuel HP, Breuel C, Emrich D, Fischer P, Gilak A, Winkler C. Changes in thyroid function after application of iodinated contrast media to normal subjects [in German]. *Med Klin.* 1979;74(41):1492-1496.
 22. Conn JJ, Sebastian MJ, Deam D, Tam M, Martin FI. A prospective study of the effect of nonionic contrast media on thyroid function. *Thyroid.* 1996;6(2):107-110.
 23. Gartner W, Weissel M. Do iodine-containing contrast media induce clinically relevant changes in thyroid function parameters of euthyroid patients within the first week? *Thyroid.* 2004;14(7):521-524.
 24. Martin FI, Tress BW, Colman PG, Deam DR. Iodine-induced hyperthyroidism due to nonionic contrast radiography in the elderly. *Am J Med.* 1993;95(1):78-82.
 25. Nygaard B, Nygaard T, Jensen LI, et al. Iohexol: effects on uptake of radioactive iodine in the thyroid and on thyroid function. *Acad Radiol.* 1998;5(6):409-414.
 26. Hintze G, Blombach O, Fink H, Burkhardt U, Köbberling J. Risk of iodine-induced thyrotoxicosis after coronary angiography: an investigation in 788 unselected subjects. *Eur J Endocrinol.* 1999;140(3):264-267.
 27. Bhan I, Dubey A, Wolf M. Diagnosis and management of mineral metabolism in CKD. *J Gen Intern Med.* 2010;25(7):710-716.
 28. Matheny ME, Shubina M, Kimmel ZM, Pendergrass ML, Turchin A. Treatment intensification and blood glucose control among hospitalized diabetic patients. *J Gen Intern Med.* 2008;23(2):184-189.
 29. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab.* 2008;93(9):3499-3504.
 30. Pantalone KM, Nasr C. Approach to a low TSH level: patience is a virtue. *Cleve Clin J Med.* 2010;77(11):803-811.
 31. Rodondi N, Newman AB, Vittinghoff E, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med.* 2005;165(21):2460-2466.
 32. Spencer C, Eigen A, Shen D, et al. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. *Clin Chem.* 1987;33(8):1391-1396.
 33. Lubin JH, Gail MH. Biased selection of controls for case-control analyses of cohort studies. *Biometrics.* 1984;40(1):63-75.
 34. Rothman K, Greenland S, Lash TL. *Modern Epidemiology.* Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
 35. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med.* 1999;130(6):461-470.
 36. Bjerre LM, LeLorier J. Expressing the magnitude of adverse effects in case-control studies: "the number of patients needed to be treated for one additional patient to be harmed." *BMJ.* 2000;320(7233):503-506.
 37. Kopp P. Thyroid hormone synthesis. In: Braverman L, Utiger RD, eds. *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text.* 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:52-68.
 38. Larsen P, Davies T, Schlumberger M, Hey I. Thyroid physiology and diagnostic evaluation of patients. In: Kronenberg H, Melmed S, Polonsky KS, Larsen PR, eds. *Williams Textbook of Endocrinology.* Philadelphia, PA: Saunders Elsevier Health Sciences; 2007:301-318.
 39. Burman KD, Wartofsky L. Iodine effects on the thyroid gland: biochemical and clinical aspects. *Rev Endocr Metab Disord.* 2000;1(1-2):19-25.
 40. Fradkin JE, Wolff J. Iodine-induced thyrotoxicosis. *Medicine (Baltimore).* 1983;62(1):1-20.
 41. Rajatanavin R, Safran M, Stoller WA, Mordes JP, Braverman LE. Five patients with iodine-induced hyperthyroidism. *Am J Med.* 1984;77(2):378-384.
 42. Vagenakis AG, Wang CA, Burger A, Maloof F, Braverman LE, Ingbar SH. Iodine-induced thyrotoxicosis in Boston. *N Engl J Med.* 1972;287(11):523-527.
 43. Mortensen JD, Woolner LB, Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. *J Clin Endocrinol Metab.* 1955;15(10):1270-1280.
 44. Leger AF, Massin JP, Laurent MF, et al. Iodine-induced thyrotoxicosis: analysis of eighty-five consecutive cases. *Eur J Clin Invest.* 1984;14(6):449-455.
 45. Savoie JC, Massin JP, Thomopoulos P, Leger F. Iodine-induced thyrotoxicosis in apparently normal thyroid glands. *J Clin Endocrinol Metab.* 1975;41(4):685-691.
 46. Iervasi G, Molinaro S, Landi P, et al. Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med.* 2007;167(14):1526-1532.
 47. Braverman LE, Ingbar SH. Changes in thyroidal function during adaptation to large doses of iodide. *J Clin Invest.* 1963;42:1216-1231.
 48. Dai G, Levy O, Carrasco N. Cloning and characterization of the thyroid iodide transporter. *Nature.* 1996;379(6564):458-460.
 49. Eng PH, Cardona GR, Fang SL, et al. Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. *Endocrinology.* 1999;140(8):3404-3410.

INVITED COMMENTARY

Iodine-Induced Thyroid Dysfunction

Evaluating the Risks of Iodinated Contrast Medium

In this issue of the *Archives*, Rhee et al¹ 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