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Postoperative Hypocalcemia Is Associated with Preoperative Vitamin D Deficiency

Kirkby-Bott J, Markogiannakis H, Skandarajah A, Cowan M, Fleming B, Palazzo F. Preoperative vitamin D deficiency predicts postoperative hypocalcemia after total thyroidectomy. World J Surg 2011;35:324-30.

SUMMARY

Background

A common complication of thyroid surgery is transient postoperative hypocalcemia, which occurs in up to 30% to 35% of patients. The rate of permanent hypocalcemia is thought to be <2% in the hands of experienced surgeons. The actual number of events has been estimated to be much higher in the population at large. The actual prevalence of important hypocalcemia is unknown, since there is no accepted level of calcium that defines hypocalcemia (1). Prevention of this transient event may reduce costs due to extra days of hospitalization, extra medication, additional blood tests, and outpatient visits. This study examined the relationship between preoperative vitamin D levels and postoperative calcium levels.

Methods and Results

Data were collected prospectively from 165 consecutive thyroidectomies between January 2006 and March 2009 at a premier academic hospital in London. The data were retrospectively analyzed. Patients were divided into three groups based on the preoperative total vitamin D (vitamin D2 + vitamin D3) level: group 1, <10 ng/ml; group 2, 10 to 20 ng/ml; group 3, >20 ng/ml. Hypocalcemia was defined as a postoperative calcium level (corrected for albumin) of <8 mg/dl on postoperative day 1 or 2. There were 44 cases of postoperative hypocalcemia in the 165 patients. There was a significant stepwise increased risk of transient but not permanent hypocalcemia with lower vitamin D levels. Hypocalcemia occurred in 35.4% of group 1, 28.2% of group 2, and 15.2% in group 3. Graphically and statistically, the midpoint of group 2 appeared to be the threshold of vitamin D at which the risk of hypocalcemia increased. Reforming the groups to ≤14 ng/ml and >14 ng/ml, the rate of hypocalcemia was significantly different—35.5% and 19.1%, respectively (P = 0.014 by the chi-square test). Binary logistic regression analysis of postoperative parathyroid hormone and vitamin D levels show that they are independent risk factors for hypocalcemia. The median length of the hospital stay was significantly greater (P<0.001) in those with preoperative vitamin D deficiency (<10 ng/dl; 2 days), as compared with those without vitamin D defi-

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ciency (>20 mg/dl; 1 day). The risk of hypocalcemia was not associated with the type of thyroid pathology.

Conclusions

This study shows that preoperative low serum vitamin D deficiency is a risk factor for transient but not permanent postoperative hypocalcemia. The risk was stepwise, but the threshold of the increased risk of postoperative hypocalcemia was associated with a low vitamin D level (<14 ng/ml).

ANALYSIS AND COMMENTARY

The increasing incidence of thyroid cancer has resulted in larger numbers of thyroidectomies for the treatment of malignant thyroid nodules and the diagnosis of indeterminate thyroid nodules. These surgeries are accompanied by the cost of thyroid hormone replacement medication and also the cost of unintentional complications of surgery, including transient and permanent hypocalcemia. This retrospective study had a relatively high incidence of postoperative hypocalcemia, which was defined by albumin-corrected calcium <8 mg/dl, a finding not usually associated with significant symptomatic hypocalcemia. This study is not randomized and does not examine the effect of presurgery therapy. Using these data, it cannot be determined whether low vitamin D levels caused the postoperative hypocalcemia. It does appear that the length of stay after thyroidectomy is shorter in patients with adequate vitamin D levels. It seems reasonable to make sure that preoperative vitamin D is not severely insufficient (3), and according to this study, it should be >14 ng/ml, a level that is still considered to be less than optimal for good bone health per the Institute of Medicine (IOM). I think that a target of >20 ng/ml, recommended by the IOM, is a reasonable minimal preoperative vitamin D target (4).

— Stephanie L. Lee, MD, PhD

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Malabsorption of Thyroxine Occurs in Atypical Celiac Disease and Abates on a Gluten-Free Diet

Virili C, Bassotti G, Santaguida MG, Iuorio R, Del Duca SC, Mercuri V, Picarelli A, Gargiulo P, Gargano L, Centanni M. Atypical celiac disease as cause of increased need for thyroxine: a systematic study. J Clin Endocrinol Metab. January 11, 2012 [Epub ahead of print]. doi:10.1210/jc.2011-1851.

SUMMARY

Background

The dose of L-T_4 needed to treat hypothyroidism is unexpectedly high in over 10% of patients with hypothyroidism. Noncompliance is common, but once eliminated, causes of malabsorption should be considered; one possibility is celiac disease. This autoimmune enteropathy is found more commonly in patients with Hashimoto's thyroiditis (and vice versa) than in the general population. Higher-than-usual doses of L-T_4 have been required in several cases in which hypothyroidism has occurred in patients with active celiac disease, and their L-T_4 requirement has fallen after eating a gluten-free diet. However, patients with celiac disease who have severe gastrointestinal (GI) symptoms are much less common than patients with positive antibodies and biopsies but without notable GI symptoms. The current study systematically addressed the issue in patients with "atypical celiac disease," who do not have notable GI symptoms but have iron deficiency anemia, diminished stature, low weight, or recent weight loss.

Methods

The L-T_4 dose (Eutirox, Bracco, Italy) that was needed to treat 68 middle-aged patients with Hashimoto's thyroiditis (without GI symptoms) was compared to the TSH response in 35 patients who had Hashimoto's thyroiditis but also had tissue transglutaminase and/or endomysial antibodies plus biopsy-proven celiac disease. Patients who were pregnant or taking substances or drugs known to contain iodine or to interfere with L-T_4 absorption or action, eating a gluten-free diet, or had previously known celiac disease or other relevant GI disorders were excluded. All participants took their L-T_4 while fasting and waited at least an hour before eating. The TSH level achieved in the 68 patients who only had Hashimoto's thyroiditis was compared with the TSH achieved in the 35 patients who had both Hashimoto's hypothyroidism and atypical celiac disease. The 35 patients were then put on a gluten-free diet, but only 21 were judged to be compliant with the diet. The compliant patients were kept on their previous L-T_4 dose, whereas the 14 diet-noncompliant patients had their L-T_4 dose increased by 25 µg; thyroid-function tests were repeated about every 4 months. The statistical analysis was nonparametric, based on the median of the middle two interquartile ranges, excluding 25% at each end of the spectrum of data.

Results

The baseline studies before thyroxine therapy revealed the median TSH to be higher in the 68 subjects in the control Hashimoto's group, indicating that they had more subclinical hypothyroidism (7.26 µU/ml vs. 5.7 µU/ml). Their median weight was also 10% higher than that of the group with celiac disease (66 kg vs. 60 kg). On the other hand, the median baseline FT_4 was lower in those with celiac plus Hashimoto's disease (0.91 vs. 1.12 ng/dl), indicating that they had mild hypothyroidism more commonly. The median TSH fell to 1.02 µU/ml in the 68 control patients after they took L-T_4 for about 5 months (median dose, 1.3 µg/kg). In contrast, the median TSH fell only to 4.2 µU/ml after giving L-T_4 (median dose, 1.4 µg/kg) for about 6 months to the 35 patients with celiac plus Hashimoto's disease. Furthermore, the TSH of only one patient with celiac disease fell into the target range of 0.5 to 2.5 µU/ml. The 21 who were judged to be compliant with the gluten-free diet remained on their previous L-T_4 dose (median, 1.32 µg/kg), and in every case the TSH fell, with the median TSH reaching 1.25µU/ml after about-11months. In the 14 diet-noncompliant patients, the L-T_4 dose was increased by 25 µg, and after 4 months, their median TSH also fell (1.54 µU/ml) on a median dose of 1.96 µg/kg. The higher L-T_4 requirement did not correlate with the body-mass index.

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Conclusions

Patients with atypical celiac disease may need a higher dose of L-T_4, and this increased requirement may be reversed by a gluten-free diet. Some patients with evidence of malabsorption of L-T_4 may have atypical celiac disease.

ANALYSIS AND COMMENTARY

The authors do not indicate how noncompliance with the gluten-free diet was established. Up to 20% of patients who are considered diet-compliant can have recurrent or persistent symptoms. H. pylori infection is common in such patients, but the authors do not state that the diet-noncompliant patients were tested for H. pylori or atrophic gastritis. Wide variability in TSH levels can make nonparametric analysis appropriate, but it excludes 50% of the data, so it would have been useful if each outlier had been included on the "box-and-whisker plot." It is not clear why age, weight, and L-T_4 dose did not undergo regular parametric analysis. Regardless of these quibbles, it does seem clear that the dose of L-T_4 needed to normalize the serum TSH level in some patients with "atypical" celiac disease is reduced when they adhere to a gluten-free diet.

Should every patient requiring a "higher-than-normal" dose of L-T_4 be evaluated? First of all, L-T_4 absorption varies between individuals and between tablets/capsules from different manufacturers. Obviously, noncompliance, severe obesity, pregnancy, and dietary or drug factors that influence absorption, such as antacids, calcium, or long-term proton-pump inhibitor therapy need to be ruled out. However, in cases in which it proves difficult to maintain the TSH level in the target range with high dose of L-T_4, disorders of the GI tract need to be assessed.

Malabsorption of L-T_4 can reflect atrophic gastritis (1) or—more likely—H. pylori infection. H. pylori infection was found in 32 Turkish patients in whom celiac disease and small intestinal bacterial overgrowth had been excluded and who remained hypothyroid on doses of L-T_4 above 1.6 µg/day. Eradication of H. pylori with triple or quadruple therapy reduced the mean TSH from 30.5 µU/ml to 4.2 µU/ml, and 20% of the patients actually became hyperthyroid on the dose of L-T_4 that had previously been insufficient (2). Similar findings have been reported on the L-T_4 dose required to normalize TSH levels in patients with achlorhydria or with gastric parietal-cell antibodies, or to suppress the TSH in patients with multinodular goiter if they had H. pylori infection. In addition to celiac disease, malabsorption at the level of the small intestine can occur with the short bowel syndrome, from small intestinal bacterial overgrowth (which is also found more commonly in hypothyroidism), or from infections with certain parasites like Giardia, or even from severe lactose intolerance. Finally, in 28 Argentine patients in whom several GI causes of L-T_4 malabsorption were ruled out, administering 1 g of vitamin C in a glass of water along with the L-T_4 for 6 to 8 weeks increased L-T_4 absorption significantly (3).

— Stephen W. Spaulding, MD

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Subclinical Hyperthyroidism and Subclinical Hypothyroidism Increase the Incidence of Heart Failure in Older Persons

Nanchen D, Gussekloo J, Westendorp RG, Stott DJ, Jukema JW, Trompet S, Ford I, Welsh P, Sattar N, Macfarlane PW, Mooijaart SP, Rodondi N, de Craen AJ; on behalf of the PROSPER Group. Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. J Clin Endocrinol Metab. January 11, 2012 [Epub ahead of print].

SUMMARY

Background

In many studies, subclinical thyroid dysfunction has been associated with cardiovascular disease (CVD), but there is still controversy about these associations. The purpose of this study was to examine the association between subclinical thyroid dysfunction and adjudicated cardiovascular events in a large prospective study of older people with cardiovascular risk factors or preexisting CVD.

Methods

The patient population consisted of 5316 patients who were part of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial. Patients had measurements of serum TSH and FT_4 and were categorized into one of three groups: euthyroid, subclinical hyperthyroidism based on TSH levels <0.45 mU/L with normal FT_4, or subclinical hypothyroidism based on TSH levels >4.5 mU/L with normal FT_4. Cardiovascular outcomes were defined and judged by an expert committee.

Results

The mean (±SD) age of the population was 75±3.3 years and did not differ between the three groups. Subclinical hypothyroidism was present in 199 participants (3.7%) at baseline, and 34 of them were taking thyroid hormone. Subclinical hyperthyroidism was present in 71 participants (1.3%) and 5 of them were taking thyroid hormone. The incidence rate of hospitalization for heart failure was higher during a 3.2-year follow-up period in those with subclinical hyperthyroidism, as compared with the euthyroid group (P<0.01), with a sex- and age-adjusted hazard ratio (HR) of 2.93 (95% CI, 1.37 to 6.24), and worse in those with TSH levels <0.1 mU/L (age- and sex-adjusted HR, 4.61; 95% CI, 1.71 to 12.47). In the 38 patients with subclinical hypothyroidism with TSH levels above 10 mU/L, the incidence rate of heart failure was significantly higher in the age- and sex-adjusted model as compared with euthyroid participants (HR, 3.01; 95% CI, 1.12 to 8.11).

During the 3.2-year follow-up, 9.4% had atrial fibrillation, 11.0% had myocardial infarction, and 10.3% died. There were no differences in these conditions between the euthyroid and hypothyroid groups. In the group of patients with subclinical hyperthyroidism with TSH <0.1 mU/L who were not taking pravastatin, there was significantly higher cardiovascular mortality (HR, 4.61; 95% CI, 1.71 to 12.47).

Persistent subclinical hypothyroidism with TSH above 10 mIU/L remained associated with heart failure hospitalization as compared with euthyroidism with an age- and sex-adjusted HR of 4.99 (95% CI, 1.59 to 15.67).

Conclusions

In older patients with CVD who also have subclinical hyperthyroidism, especially those with TSH <0.1 mU/L, there is an increased incidence of heart failure. In those with subclinical hypothyroidism and TSH >10 mU/L, there is an increased incidence of heart failure and hospitalization for heart failure.

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ANALYSIS AND COMMENTARY

This carefully performed retrospective European study shows that subclinical hyperthyroidism increases the incidence of heart failure in older patients with a history of CVD. The data are most impressive for those with TSH <0.1 mU/L. The mechanisms by which subclinical hyperthyroidism might contribute to heart failure include increased heart rate, larger left ventricle size, impaired diastolic function, and atrial fibrillation.

The data concerning atrial fibrillation do not confirm the study of Sawin et al. in the Framingham population in 1994 that reported a nearly 3-fold increased risk of atrial fibrillation in those with TSH <0.1 mU/L (1), but there were only 71 patients in the European group with subclinical hyperthyroidism, of whom only 28 had TSH <0.1 mU/L. The increased incidence of atrial fibrillation in subclinical hyperthyroidism was also found in another study of a large geriatric population (2). It is noteworthy that serum T_3 was not measured in the current study, so the diagnosis of T_3 thyrotoxicosis could not be assessed.

The increased incidence of heart failure in the patients with subclinical hypothyroidism is significant only for those with TSH >10 mU/L, as shown previously in the study by Rodondi et al (3). Because TSH is a modifiable risk factor, the authors recommend that elderly patients with subclinical hyperthyroidism who have TSH <0.1 mU/L and those with subclinical hypothyroidism who have TSH >10 mU/L be treated appropriately to avoid the cardiovascular consequences of these disorders.

— Jerome M. Hershman, MD

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Amiodarone May Be Continued in Patients with Amiodarone-Induced Thyroiditis Treated with Prednisone

Eskes SA, Endert E, Fliers E, Geskus RB, Dullaart RP, Links TP, Wiersinga WM. Treatment of amiodarone-induced thyrotoxicosis type 2: a randomized clinical trial. J Clin Endocrinol Metab 2012;97:499-506

SUMMARY

Background

Amiodarone causes thyrotoxicosis in two ways. First, it provides a large iodide load that can induce hyperthyroidism in susceptible individuals with underlying Graves' disease or multinodular goiter—called type 1 amiodarone-induced thyrotoxicosis (AIT). Second, it can cause thyrotoxicosis through a destructive effect on thyrocytes, a form of thyroiditis called AIT type 2. The treatments for AIT usually require discontinuation of amiodarone, in addition to other measures. The aims of the present study were to demonstrate the feasibility of continuing to administer amiodarone in AIT type 2, and to determine whether perchlorate was useful for its treatment.

Methods

Patients with AIT type 2 were recruited from 10 centers in The Netherlands. The criteria for the diagnosis were TSH <0.4 mU/L, FT_4 >25 pmol/L (1.94 ng/dl), negative anti-TPO and anti-TSH-receptor antibodies, no visualization of the thyroid on 99mTc-pertechnetate scintigraphy, absence of nodular goiter on ultrasonography, and patient consent to continue amiodarone. Patients were randomly assigned to one of three treatment groups, but physicians and patients were not blinded with regard to study medication: group A, prednisone 30 mg/day plus methimazole 30 mg/day; group B, sodium perchlorate 500 mg twice daily plus methimazole 30 mg/day; group C, prednisone 30 mg/day plus sodium perchlorate 500 mg twice daily plus methimazole 30 mg/day. Follow-up evaluation occurred at 4-week intervals to 28 weeks, then at 8-week intervals up to 2 years. Medication was adjusted based on thyroid-function tests.

Results

The number of patients randomly assigned to groups A, B, and C were 12, 14, and 10, respectively (6 of the 42 patients initially randomized were excluded because they either had stopped taking amiodarone, had moved out of the country, or had positive tests for anti-TSH receptor). The median time for FT_4 levels to reach <25 pmol/L was 4 weeks in group A and 12 weeks in the other groups, but there were no significant differences in the time to normalization of FT_4 and TSH between groups. The serum TSH normalized with the therapy in all the patients initially receiving prednisone (groups A and C), however prednisone needed to be added to 4 of the 14 patients in group B. Recurrent thyrotoxicosis occurred in 1 patient in group A at 24 weeks when he was not on therapy with prednisone and methimazole, and in 2 patients in group C at 12 and 76 weeks when they were off the triple therapy. Subclinical hypothyroidism developed in about 40% of patients.

Conclusions

Euthyroidism was reached in all patients despite the continuation of amiodarone. Prednisone remains the preferred treatment for AIT type 2 because perchlorate given alone or in combination with prednisone did not produce better outcomes.

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ANALYSIS AND COMMENTARY

In European regions with relatively low iodine intake, there is a nearly 10% incidence of AIT in patients on amiodarone. Bartalena, Martino, and associates in Italy were the first to show that prednisone was effective in the treatment of type 2 AIT (1). The main goal of the current study was to show that amiodarone could be continued while patients were undergoing therapy for type 2 AIT, and that the condition would resolve. This contradicts the usual approach of stopping amiodarone when either form of AIT occurs, as has been recently recommended (2). Bogazzi et al. reported that 5 of 7 patients who continued amiodarone during prednisone therapy for type 2 AIT relapsed after prednisone was withdrawn (3).

The decision to use methimazole for all three groups is surprising. It is the mainstay of treatment in addition to withdrawal of amiodarone in type 1 AIT, in which there is overproduction of thyroid hormone, but it is not recommended when the diagnosis of type 2 AIT is made with confidence. The Italian group has shown that methimazole is ineffective in type 2 AIT in comparison with prednisone (4).

The second aim of the current study is curious. Perchlorate was given with methimazole in group B, and with methimazole and prednisone in group C. The usual reason to administer perchlorate is to deplete the thyroid of iodide that comes from amiodarone; perchlorate is used in type 1 AIT, but not in type 2 AIT. The study showed that 71% of group B who only received perchlorate and methimazole had improvement, an unexpected finding. Nevertheless, prednisone was the more effective therapy. There are patients who are thought to have a combination of types 1 and 2 AIT. "Shotgun" therapy with prednisone and methimazole is effective in these patients, and I use it initially in patients who have severe AIT and in whom the diagnosis of type 1 versus type 2 is unclear. Interestingly, sestamibi scans may be helpful in this differential diagnosis (5). Type 1 patients take up the sestamibi tracer and type 2 patients do not.

— Jerome M. Hershman, MD

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A New Form of Congenital Hypothyroidism with Normal Serum TSH Values Has Been Reported

Bochukova E, Schoenmakers N, Agostini M, Schoenmakers E, Rajanayagam O, Keogh JM, Henning E, Reinemund J, Gevers E, Sarri M, Downes K, Offiah A, Albanese A, Halsall D, Schwabe JW, Bain M, Lindley K, Muntoni F, Khadem FV, Dattani M, Farooqi IS, Gurnell M, Chatterjee K. A mutation in the thyroid hormone receptor alpha gene. N Engl J Med 2012;366:243-9. Epub December 14, 2011.

SUMMARY

Background

Thyroid hormone receptors are encoded by two genes that undergo alternative splicing. The known subtypes of thyroid hormone receptors are TRα1 (predominantly present in bone, the gastrointestinal [GI] tract, myocardium, and the central nervous system [CNS]), TRβ1 is predominant in hepatic and renal tissue and TRβ2 in the hypothalamus, pituitary, cochlea, and retina. Thyroid hormone resistance is a rare congenital disease (present in 1 in 40,000 total population), due, in most cases, to dominant negative mutations of the TRβ gene. In a few cases, the gene defect could not be identified (1).

Until now, no clinical case of mutation of the TRα gene has been reported, and it was suggested that these mutations were lethal. However, animal models indicated that the complete absence of TRα had only minimal effects in otherwise normal mice. Homozygous dominant negative mutations of the TRα receptor were lethal; the tissues depending on TRα stimulation were greatly affected. In contrast, heterozygous animals survived, although they had significant but varying phenotypes. The authors of this article describe the first human case of a de novo TRα mutation acting in a dominant negative manner, similar to the severely affected mutated mice.

Methods and Results

A 6-year-old girl of Caucasian origin, born to unrelated parents, presented with many of the stigmata of severe congenital hypothyroidism, including growth and developmental retardation, skeletal dysplasia, and extremely severe constipation. Physical examination revealed a large head and short legs. She had had delayed tooth eruption and, at 6 years of age had no secondary dentition. Her gait was slow, broad-based, and clumsy. The size of the thyroid was not mentioned. Radiographs showed multiple extra bone pieces (wormian bones) of the skull with a patent sagittal suture and alterations of the hip typical for hypothyroidism. X-rays indicated a markedly dilated bowel. Her heart rate was below the 10th percentile and her blood pressure was also low. The biochemical parameters showed a markedly decreased total and FT_4 and a high total T_3 and FT_3, and reverse T_3 was practically absent. The ratio of T_4 to T_3 was very low. Most interestingly, serum TSH was strictly normal (1.04 mU/L). As a marker of TRβ overactivity, serum hormone binding globulin was clearly increased even before treatment with thyroxine. Attempts at treating the patient with thyroxine were not successful, since the TRα-dependent parameters, such as heart rate, blood pressure, and metabolic rate responded poorly or not at all. However, serum TSH was completely suppressed, reflecting the normal functioning of TRβ-mediated thyroid hormone effects.

The mutation was identified by a method called "whole exome capture," rather than the cumbersome sequencing of the whole genome. A heterozygous nonsense mutation (E403X) was identified in TRα1, which was not present in either parent. Transfection studies in JEG-3 cells revealed the dominant negative character of this receptor. In other words, in the presence of a mutated receptor, the normal TRα could not be activated by T_3.

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Conclusions

The clinical presentation of this 6-year-old child could easily be confounded with the appearance of classical hypothyroidism characterized by growth and developmental retardation, skeletal dysplasia and extremely severe constipation. However, the biochemical data showed a normal serum TSH with low normal FT_4 and a high normal FT_3. Similar biochemical data can be found in the Allan–Herndon–Dudley syndrome, but the phenotype is completely different. This syndrome is due to a defect of a thyroid hormone transporter (2). The disease described here is due to a dominant negative mutation of the TRα gene (E403X). The patient was a heterozygote. The clinical phenotype could not be improved by L-T_4 treatment. It is likely that this syndrome is extremely rare. Interestingly, patients with thyroid hormone resistance due to TRβ mutations have a completely different clinical picture, often with some signs of tissue hyperthyroidism, such as rapid heart rate.

ANAYLSIS AND COMMENTARY

It is amazing how accurately genetic studies in mice predicted the human disease, in particular the TRα1(PV) mutant mouse, which shows marked growth retardation (3). While the absence of a functioning TRα gene has few phenotypic and biochemical consequences in mice (4), some dominant negative mutants produced mouse phenotypes similar to the human case (5). In mice, the homozygotes were lethal, whereas the heterozygotes were viable.

In the present patient, the lack of response to relatively high doses of L-T_4 is astonishing. It indicates that the mutation has a strong dominant effect. In patients with TRβ mutations, L-T_4 and/or Triac may improve the hyperthyroid state, but only in some cases. This indicates that the expression of the defect can vary greatly.

Can we make any deductions from this case concerning the treatment of the average patient with hypothyroidism? One may think about tissue-specific effects, but for the moment this remains speculative.

— Albert G. Burger, MD

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Correlation of Maternal Thyroid Parameters During the First Half of Pregnancy and Cord Thyroid Parameters: Are They Associated with Adverse Pregnancy and Child Neuropsychological Outcomes?

Medici M, de Rijke YB, Peeters RP, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VV, Hofman A, Hooijkaas H, Steegers EA, Tiemeier H, Bongers-Schokking JJ, Visser TJ. Maternal early pregnancy and newborn thyroid hormone parameters: the Generation R Study. J Clin Endocrinol Metab 2012;97;646-652].

SUMMARY

Background

A number of studies have analyzed the effects of maternal thyroid status during pregnancy and mental and motor development of the child. However, limited data are available on the relation between maternal thyroid hormone (TH) levels during pregnancy and fetal TH levels. The authors' objective was to study maternal thyroid parameters during the first half of pregnancy as well as their relation to cord thyroid parameters.

Methods

This study was embedded in the Generation R Study, a population-based cohort from early fetal life onward in Rotterdam, The Netherlands. Mothers with a delivery date between April 2002 and January 2006 were enrolled in the study. Data on serum TSH, FT_4, and T_4 levels were complete for 5186 pregnant women after excluding those with thyroid disease who were on medication, those who had twin pregnancies, and those whose pregnancies were the result of fertility treatment. Maternal serum samples were obtained in early pregnancy (mean [±SD], 13.3±1.7 weeks), and cord serum samples (available in 3036 newborns) were obtained at birth (39.9±1.9 weeks), with the exclusion of those delivered at a gestational age less than 37 weeks.

Results

Reference ranges for maternal TSH, FT_4, T_4, and cord TSH and FT_4 levels were defined as the range between the 2.5th and 97.5th percentiles. Ranges for the first and second trimesters were 0.01 to 4.00 and 0.05 to 4.05 mU/L for TSH, 10.86 to 24.00 and 10.28 to 21.50 pmol/L for FT_4, and 89.9 to 210.0 and 97.8 to 221.0 nmol/L for T_4. In the first trimester, 8.6% of the women with TSH levels in the normal range had a TSH level >2.5 mU/L. In the second trimester, 4.9% of the women with TSH levels in the normal range had a TSH level >3.0 mU/L.

TPOAb positivity was associated with higher maternal TSH levels, lower FT_4 levels, an 8-fold higher risk of subclinical hypothyroidism, and a 26-fold higher risk of overt hypothyroidism.

Maternal and cord TSH levels were positively correlated, as were maternal and cord FT_4 levels. Associations remained similar after the exclusion of TPOAb-positive mothers and additional correction for smoking, socioeconomic status, and ethnicity.

Conclusions

The authors observed a positive correlation between maternal and cord thyroid parameters, a substantial number of women with TSH levels above 2.5 and 3.0 mU/L in the first and second trimesters, respectively, and a significantly increased risk of hypothyroidism in TPOAb-positive mothers.

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ANALYSIS AND COMMENTARY

The study had three observations of clinical interest. First, the authors mentioned the limited data available on the relations between maternal TH parameters during pregnancy and fetal TH levels. Few studies have analyzed these associations in mothers who had no known thyroid abnormalities but did not find any associations; however, sample sizes were either limited (1) or neonatal TH parameters were determined 2 days after birth, a time at which associations are likely to be influenced by the neonatal TSH surge (2). The authors found a positive correlation between maternal (early in pregnancy) and cord-blood serum TSH and FT_4 measured in 2563 mother–child pairs from euthyroid mothers. These associations could in part be explained by the placental transfer of T_4 as well as by shared factors between mother and child, which are known to influence thyroid parameters, such as genetics and nutrition (e.g., iodine intake). Further studies are needed to correlate maternal and cord-blood thyroid parameters and subsequent neuropsychological development in the child.

Second, serum TSH, FT_4, and T_4 were measured in 5393 pregnant women in an iodine-sufficient population after the exclusion of women with TPOAb positivity, known thyroid disease, use of thyroid-interfering medication, twin pregnancies, and pregnancies after fertility treatment. A TSH level >2.5 mU/L was found in 8.6% of women in the first trimester and a level >3.0 mU/L in 4.9% of women in the second trimester. The authors underlined the importance of using population-specific reference ranges in the diagnosis of thyroid dysfunction in pregnancy, because following the recent recommendations of the ATA guidelines, these women would have been diagnosed as "hypothyroid" (3).

Third, the authors confirmed a previous study of a substantially increased risk of both subclinical and overt hypothyroidism in TPOAb-positive mothers (4). This finding is of significant clinical importance in relation to euthyroid women with Hashimoto's thyroiditis who are planning a pregnancy, in which case a preconception serum TSH level close to 1 mIU/L would be desirable to prevent the development of hypothyroidism early in pregnancy.

— Jorge H. Mestman, MD

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Clinical THYROIDOLOGY
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Radioiodine Lobe Ablation May Be an Effective Alternative to Completion Thyroidectomy in Selected Patients with Minimally Invasive Follicular Thyroid Cancer

Barbesino G, Goldfarb M, Parangi S, Yang J, Ross DS, Daniels GH. Thyroid lobe ablation with radioactive iodine as an alternative to completion thyroidectomy after hemithyroidectomy in patients with follicular thyroid carcinoma: long-term follow-up. Thyroid. December 27, 2011 [Epub ahead of print].

SUMMARY

Background

Follicular thyroid cancer constitutes about 10% of thyroid cancers and is difficult to diagnose on fine-needle aspiration biopsy (FNAB). Many patients with FNAB diagnosis of follicular lesions undergo hemithyroidectomy, and only a small proportion of these lesions turn out to be follicular carcinomas. Subsequent treatment is usually a completion thyroidectomy, or uncommonly, ^{131}I ablation of the residual lobe. The latter procedure may be used in patients who have recurrent laryngeal-nerve palsy from the surgery or in those who refuse further surgery. The purpose of the current retrospective study was to review the outcome of patients who underwent radioiodine ablation after hemithyroidectomy (RAI-L-ABL) and compare them with patients who had completion thyroidectomy (C-Tx) and those who had initial total thyroidectomy (T-Tx) for follicular thyroid cancer.

Methods

The study included patients who were followed at the Thyroid Unit of the Massachusetts General Hospital. There were 37 patients in the RAI-L-ABL group treated, from 1983 through 2007, with 30 to 32 mCi ^{131}I to ablate the remaining lobe; there were 68 patients in the C-Tx group and 29 in the T-Tx group, followed from 1993 through 2007. In this retrospective study, follow-up procedures were not uniform over time. Patients were followed using clinical observation, radioiodine scans, and thyroglobulin measurements.

Results

Seven patients in the RAI-L-ABL group reported mild to moderate neck tenderness after the ablative dose. After thyroid hormone withdrawal, the mean (±SD) radioiodine uptake in the RAI-L-ABL group (0.6±0.8%) was lower than those of the C-Tx (2.0±3.3%) and T-Tx (1.3±1.8%) groups. Based on radioiodine scans showing residual thyroid tissue, 12 of the 37 patients in the RAI-L-ABL group received an additional dose of about 100 mCi ^{131}I. Radioiodine remnant ablation was given to 86% of the other two groups.

Anti-Tg antibodies were present in 46.5%, 13%, and 17% of the RAI-L-ABL, C-Tx, and T-Tx groups, respectively ($P<0.05$). After withdrawal of thyroid hormone, serum Tg concentrations did not differ between the three groups and were elevated in 27%, 24%, and 14% of the RAI-L-ABL, C-Tx, and T-Tx groups, respectively. The mean withdrawal serum TSH in the RAI-L-ABL group was 83 mU/L and TSH was >25 mU/L in all patients, indicating a lack of functional thyroid tissue. At last follow-up, detectable serum Tg was found in 38% of the RAI-L-ABL group, 14% of the C-Tx group, and 28% of the T-Tx group.

Median follow-up was longer (95 months) in the RAI-L-ABL group than in the C-Tx (47 months) and T-Tx (53 months) groups. One disease-specific death of a patient known to have distant metastatic disease before surgery occurred in the RAI-L-ABL group. Another death occurred in a patient in the T-Tx group due to pulmonary metastases. Two additional C-Tx patients and two T-Tx patients were alive with distant metastatic disease at the end of follow-up. The staging of patients at the last available clinical observation did not differ between groups.

Conclusions

Radioactive remnant iodine ablation, completion thyroidectomy, and total thyroidectomy result in similar long-term outcomes in the treatment of follicular thyroid cancer.

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ANALYSIS AND COMMENTARY

For minimally invasive thyroid carcinoma without significant vascular invasion, lobectomy may be sufficient. Unlike papillary thyroid carcinoma, follicular carcinoma is rarely bilateral. In instances in which the follicular carcinoma is widely invasive, removal of all thyroid tissue is clearly indicated and radioiodine lobe ablation is considered to be far less desirable than completion thyroidectomy, usually without node dissection. The ATA guidelines recommend against radioiodine lobe ablation (recommendation 30) but do not distinguish between papillary and follicular thyroid carcinoma in this recommendation (1). Because follicular thyroid cancer results in vascular invasion and distant metastases and has a higher mortality than papillary thyroid cancer (2), total thyroidectomy is recommended (2). This is followed by radioiodine ablation of remnant tissue.

The current retrospective study shows that radioiodine remnant ablation is effective; unfortunately, the groups are not truly comparable because the RAI-L-ABL group was treated in an earlier time period. The higher proportion of detectable Tg may be related to treating fewer of this group with a subsequent ablative dose of ^{131}I; the basis for this was lower thyroid uptake of a diagnostic dose of ^{131}I after the lobe ablation in this group. Although the authors state that more of the RAI-L-ABL patients had anti-Tg antibodies, possibly induced by the ^{131}I therapy for ablation of the lobe, they do not provide data on the final proportion with antibodies.

When patients refuse to have completion thyroidectomy or when the surgeon is reluctant to perform it because of recurrent laryngeal-nerve palsy, radioiodine ablation may be an effective alternative. The outcome data with regard to mortality are reassuring in this respect when these three groups were compared.

— Jerome M. Hershman MD

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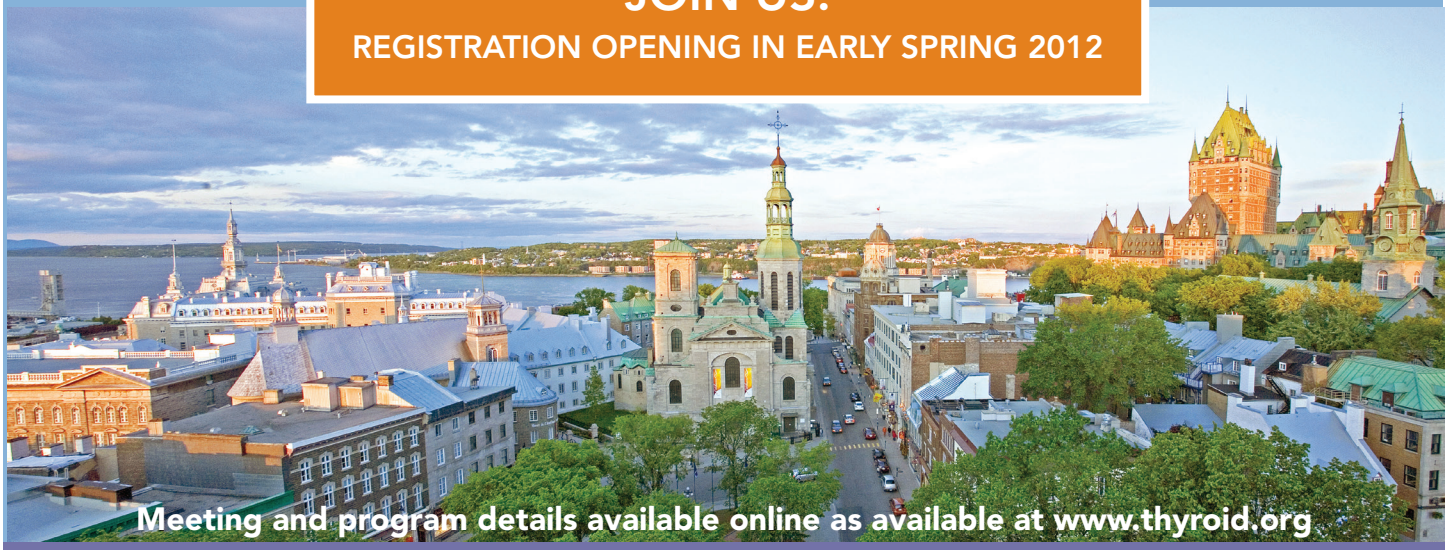

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