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Can Moderate Alcohol Consumption Reduce the Prevalence of Hypothyroidism? A Review of Three Recent Papers

SUMMARIES

Background

Three new studies suggest that moderate alcohol consumption is associated with a decreased incidence/prevalence of overt hypothyroidism. A 5-year study cohort from Amsterdam for prospectively studying the course of euthyroid subjects whose relatives have autoimmune thyroid diseases (AITDs), was now used to assess the annual incidence of overt hypothyroidism in subjects who consumed more than 10 drinks per week versus those who did not. A study cohort of Danish subjects originally designed to assess how increasing iodine intake affected thyroid diseases was now used retrospectively to analyze the effect of alcohol consumption on the prevalence of hypothyroidism. Finally, a study from the Cleveland Clinic retrospectively assessed the prevalence of hypothyroidism in patients who consumed fewer than 10 drinks per week versus those who abstained completely, in patients with biopsy-proven non-alcoholic fatty liver disease (NAFLD) versus control patients with normal liver function.

STUDY 1

Effraimidis G, Tijssen JGP, Wiersinga WM. Alcohol consumption as a risk factor for autoimmune thyroid disease: a prospective study. Eur Thyroid J 2012;1:99-104.

Methods

A cohort of euthyroid women who had at least one family member with an AITD was followed yearly for 5 years. The authors compared the yearly incidence of overt hypothyroidism in those who consumed more than 10 alcoholic drinks per week with those women consumed less or no alcohol, matching each with two control subjects from the same cohort in whom overt hypothyroidism did not develop, based on duration of follow-up, age, and current smoking (but apparently not on obesity, liver function or comorbid conditions). At baseline, the TSH levels were significantly higher and the free T_4 levels were lower in those who were later to become overtly hypothyroid (1).

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Results

A total of 38 cases of overt hypothyroidism occurred during the 5-year follow-up period. At the beginning of the study, the proportion of patients who subsequently had become hypothyroid and who consumed more than 10 alcoholic drinks per week (3 of 38) was not significantly different from the proportion in the controls (11 of 76) (8.3% vs. 14.5%, P = 0.36 by Student's t-test). Interestingly, in the year before hypothyroidism developed, the proportion of patients consuming more than 10 drinks per week fell (to 2 of 38) while the proportion rose in the controls (15 of 76) (5.3% vs. 19.7%, P<0.05). In the year that hypothyroidism appeared, "2.5" of 38 patients with hypothyroidism consumed more than 10 drinks per week versus 18 of 76 controls (6.7% [sic] vs. 23.7%, P<0.05). At baseline, the odds ratio (OR) of consuming 10 or more alcoholic drinks but still having hypothyroidism was 0.54 (95% CI, 0.14 to 2.06). The OR fell to 0.23 (95% CI, 0.05 to 1.04) in the year before the hypothyroidism developed and remained at 0.23 (95% CI, 0.05 to 1.06) in the year that hypothyroidism appeared. If the group of patients who consumed no alcohol was separated from the group who consumed fewer than 10 drinks per week, no significant differences were found between cases and controls. (In a separate study on this cohort, alcohol consumption was not associated with de novo development of anti-TPO antibodies).

Conclusions

At baseline, 3 of the 38 patients in whom hypothyroidism developed and 11 of the 76 subjects in whom it did not develop were moderate alcohol drinkers. The year before she had hypothyroidism, 1 of the 3 drinkers reduced her drinking below the moderate level, whereas in the 76 matched controls who did not become hypothyroid, the number of moderate alcohol consumers increased progressively. Although the findings suggest that moderate alcohol consumption may be protective, a single patient who stopped drinking and then had hypothyroidism may have had a substantial impact on the results.

STUDY 2

Carle A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen L, Jørgensen T, Laurberg P. Moderate alcohol consumption may protect against overt autoimmune hypothyroidism—a population-based case-control study. Eur J Endocrinol. July 16, 2012 [Epub ahead of print]. doi: 10.1530/EJE-12-0356.

Methods

Continual monitoring of all thyroid-function tests done in two areas of Denmark permitted identification of some 600 new cases of spontaneous overt hypothyroidism out of some 500,000 individuals who were tested between 1997 and 2000. The incidence was higher in northern Copenhagen, where iodine intake was only mildly low, as compared with central Aalborg, where iodine intake was moderately low (2). For each of 140 patients with newly diagnosed hypothyroidism (apparently selected randomly), four euthyroid controls were identified, matched for sex, age and geographic region. Most of the controls for female cases came from tightly selected age groups, and for the male cases controls came from a single age group (60 to 65), although additional controls outside these ages were also used. When a potential control subject was identified, a blood sample was drawn and TSH was tested to ensure it was normal. In addition to an estimation of alcohol intake, any history of smoking, previous diseases, education, and hypothyroidism in family members was obtained by questionnaire. The possible association of each variable with the development of hypothyroidism was assessed using conditional logistic-regression models.

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Results

The average amount of alcohol consumed by the patients who eventually became hypothyroid was significantly less than the amount consumed by the controls (~36 g vs. ~60 g per week; P = 0.002). After correcting for smoking, comorbid conditions, education, and family history of hypothyroidism (but not time of onset), multivariate regression analysis showed that mild and moderate consumption of alcohol was associated with a reduced risk for hypothyroidism spontaneously developing. In the 35 patients who reported no recent alcohol consumption, the OR for the development of hypothyroidism was twice (2.12; 95% CI, 1.31 to 3.4) that in patients who consumed 1 to 10 units of ethanol per week (n = 85). The OR was even lower (0.47; 95% CI, 0.24 to 0.92) for those consuming 11 to 20 units of ethanol per week (n = 11). In contrast, the OR for those consuming 21 or more units of ethanol per week (n = 9) was the same as for those consuming 1 to 10 units (0.97; 95% CI, 0.44 to 2.11). Subgroup analysis revealed that abstainers were 2.17 (95% CI, 1.35 to 3.57) times more likely to have hypothyroidism develop than those who drank any alcohol. Alcohol consumption was not significantly protective in those over 60 years of age. No association was found with the type of alcohol consumed.

Conclusions

During a time when iodine intake and the incidence of spontaneous hypothyroidism were increasing in this cohort (2), the level of alcohol consumed was negatively associated with the prevalence of hypothyroidism. It should be noted, however, that the dose–response curve became U-shaped for those who consumed more than 21 drinks per week, Alcohol is known to affect a variety of immune responses, but no clear-cut mechanism for its protective effects on autoimmune disorders such as rheumatoid arthritis has been identified.

STUDY 3

Pagadala MR, Zein CO, Dasarathy S, Yerian LM, Lopez R, McCullough AJ. Prevalence of hypothyroidism in nonalcoholic fatty liver disease. Dig Dis Sci 2012;57:528-34. Epub December 20, 2011.

Methods

Of 246 consecutive patients with biopsy-proven NAFLD seen in the hepatology outpatient clinic at the Cleveland Clinic, 233 could be matched with controls chosen from general medical outpatients who had no evidence of liver disease. Based on age, sex, race, and body-mass index, 197 patients could be matched to 2 controls, while the remaining 36 patients could be matched to only 1 control. Men consuming more than 14 drinks of ethanol per week, or women consuming more than 7 drinks per week and any patients with evidence of coexisting chronic liver disease were excluded.

Results

Of the patients with NAFLD, 49 233 (21%) were taking L-T_4 and had a clinical diagnosis of hypothyroidism, while only 9.5% (41 430) of the matched controls had hypothyroidism. The mean TSH level in the patients with hypothyroidism and NAFLD was normal (3.1 mU/L), but was significantly higher than in the euthyroid NAFLD patients (2.0 mU/L, P<0.01). About 55% of the euthyroid patients with NAFLD consumed mild-to-moderate amounts of alcohol, whereas only 25% of the patients with hypothyroidism and NAFLD were mild-to-moderate alcohol consumers (P<0.001). Multivariate logistic-regression analysis showed that mild-to-moderate alcohol use was associated with a significantly lower prevalence of hypothyroidism (OR, 0.37; 95% CI, 0.18 to 0.77; P<0.01). The risk of hypothyroidism was slightly associated with body-mass index (OR 1.04; 95% CI, 1.002 to 4.6).

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Conclusions

Hypothyroidism has been found to be more common in patients with fatty liver, and it is of particular interest that alcohol consumption can reduce the prevalence of fatty liver, which may be present in up to 30% of the general population (3). The current paper indicates that moderate alcohol consumption also decreases the prevalence of hypothyroidism in patients whose fatty liver apparently does not reflect overconsumption of alcohol.

ANALYSIS AND COMMENTARY

Although these studies have limitations and the numbers of subjects involved are relatively small, their conclusions support one another. No specific value can be given for "moderate alcohol intake," since an individual's alcohol metabolism depends on environmental factors, such as one's current intestinal flora, as well as on genetic polymorphisms that affect the activity of enzymes involved in alcohol and aldehyde metabolism. Even a teetotaler's liver is exposed to the trace amounts of the endogenous alcohols produced in the gut. Assuming there is no previous history of alcohol abuse, moderate alcohol consumption is now accepted as reducing all-cause and cardiovascular mortality, and it also can reduce the incidence of certain diseases. The metabolic changes produced by moderate alcohol consumption include increased circulating levels of adiponectin, high-density lipoprotein cholesterol, apolipoprotein A1 and C-reactive protein, as well as decreased levels of fibrinogen, but clear-cut connections to any of the protective effects of alcohol remain to be established.

— Stephen W. Spaulding, MD

References

1. Effraimidis G, Strieder TG, Tijssen JG, Wiersinga WM. Natural history of the transition from euthyroidism to overt autoimmune hypo- or hyperthyroidism: a prospective study. Eur J Endocrinol 2011;164:107-13, Epub October 18, 2010.
2. Carlé A, Laurberg P, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, Jorgensen T. Epidemiology of subtypes of hypothyroidism in Denmark. Eur J Endocrinol 2006;154:21-8.
3. Hamaguchi M, Kojima T, Ohbora A, Takeda N, Fukui M, Kato T. Protective effect of alcohol consumption for fatty liver but not metabolic syndrome. World J Gastroenterol 2012;18:156-67.

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Subclinical Hypothyroidism May Spontaneously Revert to Euthyroidism in Elderly Patients Negative for TPO Antibodies

Somwaru LL, Rariy CM, Arnold AM, Cappola AR. The natural history of subclinical hypothyroidism in the elderly: the cardiovascular health study. J Clin Endocrinol Metab 2012;97:1962-9. Epub March 21, 2012.

SUMMARY

Background

Subclinical hypothyroidism (SH) is common in the elderly and there is controversy about the efficacy of therapy for this condition, although a number of studies have shown that SH is associated with cardiovascular risk factors that are improved by therapy with levothyroxine (1). The criteria for subclinical hypothyroidism have varied to some extent based on what the upper limit of normal is for serum TSH in the elderly (2), as reviewed in last month's issue of Clinical Thyroidology (3). Several reports have shown that the serum TSH may return to normal without therapy in a significant proportion of patients with SH. The authors of the current paper have used data from a large study of community-dwelling individuals 65 years of age or over to demonstrate the natural history of SH over a 4-year period, including the rates of persistence, resolution, and progression of subclinical thyroid dysfunction at 2 and 4 years.

Methods

Subjects were community-living people over age 65 in 4 U.S. areas who were in the Cardiovascular Health Study.

Subclinical hypothyroidism was defined as a TSH of 4.5 to 19.9 mU/L, with a normal free T_4 concentration.

Results

At baseline, 3996 individuals had thyroid-function tests; 402 were excluded because they were taking thyroid medication. Of the remaining 3594 subjects, 459 (12.8%) had SH (median TSH, 6.7 mU/L) and 22 (0.6%) had overt hypothyroidism. At baseline, 69% of the SH had a TSH between 4.5 and 6.9 mU/L, 20% had a TSH between 7.0 and 10 mU/L, and 11% had a TSH >10 mU/L.

Mortality was similar in those who were euthyroid and those who had subclinical hypothyroidism at baseline at either 2 years (5.3 vs. 5.9%) or 4 years (12.9 vs. 12.6%) of follow-up.

After 2 years, the incidence of SH in those who were euthyroid was 2.7%. In the SH group, 369 of 459 were available for evaluation: 56% (208) continued to have SH, 35% (128) reverted to euthyroidism, 2% (8) became overtly hypothyroid, and 7% (25) were treated with thyroid hormone. Of those with baseline TSH levels of 4.5 to 6.9 mU/L, 46% became euthyroid at 2 years, in contrast with only 7% of those who had TSH levels >10 mU/L. Progression to overt hypothyroidism occurred in 10% of those with TSH levels >10 mU/L. There was no difference in progression based on age (65–75 vs. >75 years) or sex. Thirty-five percent of those with SH had positive TPO antibody, and these subjects were less likely to revert to euthyroidism (15% vs. 48% if TPO-negative).

Of the SH group who had thyroid tests at year 4, 58% (62 of 107) of those who were euthyroid at year 2 remained euthyroid at year 4, 38% (41 of 107) of those who were euthyroid at year 2 returned to SH at year 4, and 76% (122 of 161) of those with persistent SH at year 2 continued to have SH at year 4.

Conclusions

Subclinical hypothyroidism persists for 4 years in just over half of older individuals, with high rates of reversion to euthyroidism in individuals with lower TSH concentrations and negative TPO antibody.

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ANALYSIS AND COMMENTARY

This is the largest study of an elderly cohort that examined the natural history of subclinical hypothyroidism. The conclusions are likely to be valid even though for about 10% of the SH group sera was not available for testing at 2 years. The results are similar to the Spanish study of 107 patients over 55 years of age who had SH (4) that reported 37% of patients reverted to a euthyroid state during a follow-up of 6 months to 6 years; they also found that progression to overt hypothyroidism was related to the height of the baseline serum TSH.

In regard to therapy for SH, these data provide some reassurance that the current clinical practice of treating those with TSH levels >10 mU/L and positive anti-TPO is reasonable because these patients are much more likely to progress to overt hypothyroidism.

Would the results be different if the upper limit of serum TSH was age-adjusted? If the upper TSH limit was in the range of 5 to 6 mU/L, then the population of those with SH would be smaller, especially the group with TSH levels of 4.5 to 6.9 mU/L who had the highest reversion to normal. Regardless of the cutoff for classification, those with mild elevations of serum TSH need to be retested before they are consigned to long-term therapy with levothyroxine. Another study by the Spanish group showed that a large majority of the normalization of the serum TSH occurred within the first 2 years of follow-up (5), a finding that is consistent with the current study.

— Jerome M. Hershman, MD

References

1. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev 2008;29:76-131. Epub November 8, 2007.
2. Boucai L, Hollowell JG, Surks MI. An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. Thyroid 2011; 21: 5-11. Epub November 8, 2010.
3. Kahapola-Arachchige KM, Hadlow N, Wardrop R, Lim EM, Walsh JP. Age specific TSH reference ranges have minimal impact on the diagnosis of thyroid dysfunction. Clin Endocrinol (Oxf). June 15, 2012 [Epub ahead of print]. doi:10.1111/j.1365-2265.2012.04463.x
4. Díez JJ, Iglesias P. Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. J Clin Endocrinol Metab 2004;89:4890-7.
5. Díez JJ, Iglesias P, Burman KD. Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 2005;90:4124-7. Epub April 5, 2005.

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Should We Treat Patients with Hypothyroidism with T_4 and T_3 Instead of T_4 Alone?

Ito M, Miyauchi A, Morita S, Kudo T, Nishihara E, Kihara M, Takamura Y, Ito Y, Kobayashi K, Miya A, Kubota S, Amino N. TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodothyronine levels in patients who have undergone total thyroidectomy. Eur J Endocrinol, June 18, 2012 [Epub ahead of print].

SUMMARY

Background

The mean serum TSH of a normal population is 1.4 to 1.6 mU/L, with the range varying from 0.4 to 3 or 4. It is generally accepted that serum TSH levels within these reference values indicate an adequate substitution with thyroxine in patients with hypothyroidism. With thyroxine treatment, all available T_3 has to be generated by conversion from T_4, while in normal subjects approximately 10 to 20% of T_3 is provided by thyroidal secretion. It is well established that the control of serum TSH is a very complex mechanism. In the pituitary there is an active local conversion of T_4 to T_3 and circulating T_3 probably plays a minor role in governing TSH secretion. Therefore, a slight decrease of serum T_3 levels may be of little importance for adequate pituitary function, the local T_4 concentration being the decisive factor. This raises the question of whether using serum TSH as the only monitor of adequate thyroid substitution is a fully adequate procedure. Comparing serum FT_4 and FT_3 concentrations in subjects who undergo thyroidectomy offers an excellent opportunity to test circulating thyroid hormone levels versus TSH secreted by the pituitary. The many patients with thyroid cancer who are treated with different doses of thyroxine with the aim of achieving serum TSH levels appropriate to control the disease are an ideal population in which to address this problem. This is particularly true if preoperative thyroid hormone levels are available, as they were in Ito et al.'s study.

Methods and Results

This was a retrospective study of 135 patients with thyroid cancer. Blood samples were obtained on two occasions before operation. The sample was deep-frozen. Patients with any possible interfering factor (thyroid disease other than a nodule, thyroid antibodies, any nonthyroid disease and or interfering drug treatment) were excluded. The mean dosage of thyroxine was approximately 2 μg per kilogram of body weight, adjusted according to the presumed prognosis of the thyroid cancer. Postoperative samples were obtained after at least 3 to 6 months of stable treatment and approximately 2 to 4 hours after the ingestion of thyroxine. At the end of the study, all serum FT_3 levels were remeasured from the deep-frozen samples in one single assay.

The serum TSH levels were stratified as follows: group 1: <0.03 mU/L; group 2: 0.03 to 0.3 mU/L; and group 3: 0.3 to 3 mU/L; each group corresponded to the specific risk group of thyroid cancers.

As expected, after operation serum FT_4 levels were higher than before operation. The patients with serum TSH levels of <0.03 mU/L had clearly increased serum FT_3 levels. Yet, in the group with moderately decreased serum TSH levels (0.03 to 0.3 mU/L), serum T_3 levels were identical to those before treatment (before, 3.01 ng/L; after, 2.98; for FT_4, 10.1 vs. 13.9 ng/L) and with serum TSH levels in the normal range (0.3 to 3 mU/L), serum FT_3 levels were significantly lower than before operation.

Conclusions

In this well-conducted study the authors compared serum FT_3 levels before and after total thyroidectomy followed by thyroxine treatment. Their findings indicate that FT_3 levels are equal those before operation only if serum TSH is in the slightly decreased range, between 0.03 and 0.3 mU/L. Serum TSH levels from 0.3 to 3 mU/L went along with a mean FT_3 of 2.62 ng/L, a small but significant dif-

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ference from 3.08 ng/L. The clinical significance of this difference is difficult to appreciate since the informative value of clinical testing of well-being is limited. The article, however, stresses the point that the definition of adequacy of thyroxine treatment is different if it is based on serum TSH or on peripheral thyroid hormones.

ANALYSIS AND COMMENTARY

The study has great merit insofar as serum FT_3 levels were measured altogether in one single essay. The interassay variability is therefore excluded. The absolute values may vary from one laboratory to another but for this particular study, this is irrelevant. The study was done in patients with thyroid cancer who were scheduled for surgery. Thus, preoperative values were readily available. The therapeutic goal in these patients is not a perfect euthyroid state but a suppressed serum TSH that can be obtained only with a supraphysiological thyroxine dosage. The data show that there is a small but significant imbalance between the circulating hormones and TSH levels. Indeed, within the normal range of serum TSH, defined here as values from 0.3 to 3 mU/L, serum T_3 levels were slightly decreased while serum T_4 levels were higher than in a normal population. This is most likely the consequence of the all-important mechanism of local T_4 conversion in the pituitary as opposed to the periphery. In normal persons the T_3 secreted by the thyroid is compensating for the difference. In patients with low-risk cancers and in primary hypothyroidism it is usual to adjust thyroxine therapy according to serum TSH levels, which need to be within the normal range. This is justified by the possible side effects of long-term subclinical hyperthyroidism, such as atrial fibrillation and osteopenia. On the other hand, a slightly decreased serum T_3 level has no measurable clinical manifestations. Some patients may report the inadequateness of thyroid hormone treatment despite normal serum TSH, yet our means to document such reports by clinical tests of thyroid hormone action are for the moment nonexistent. Nevertheless, it is interesting that the European Thyroid Association has addressed this question on their website.

The authors do not discuss the possible role of the frankly increased FT_4 levels. T_4 is considered a prohormone, yet it has some direct effects, such as the inactivation of deiodinase type II. Therefore, if biochemically the aim is to achieve a perfect substitution, then a combination treatment of thyroxine and triiodothyronine may be necessary.

As for the science, as a clinician I am inclined to consider this small difference in serum T_3 levels as clinically insignificant and therefore to routinely use levothyroxine as the sole treatment for hypothyroidism. Some patients are not satisfied with the treatment; rarely, I may add 12.5 μg of triiodothyronine.

— Albert G. Burger, MD

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Subclinical Hyperthyroidism Is Associated with Increased Coronary Heart Disease Mortality and Atrial Fibrillation

Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, Iervasi G, Åsvold BO, Sgarbi JA, Völzke H, Gencer B, Maciel RM, Molinaro S, Bremner A, Luben RN, Maisonneuve P, Cornuz J, Newman AB, Khaw KT, Westendorp RG, Franklyn JA, Vittinghoff E, Walsh JP, Rodondi N; Thyroid Studies Collaboration. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med 2012;172:799-809.

SUMMARY

Background

Subclinical hyperthyroidism has been associated with atrial fibrillation (AF), but studies of its associations with adverse cardiovascular outcomes have been conflicting. The current study is a large, carefully performed analysis of prospective cohort studies of subclinical hyperthyroidism (SHyper) to determine its association with coronary heart disease (CHD), CHD mortality, and atrial fibrillation.

Methods

A systematic literature search was conducted of prospective original studies of endogenous SHyper published up to June 2011. SHyper was defined as TSH <0.45 in a sensitive assay with normal FT_4 and no elevation of T_3 or FT_3. Studies had to include data on incident CHD, related demographic factors, and mortality. Primary analyses were adjusted for age and sex and then further adjusted for traditional cardiovascular risk factors: systolic blood pressure, current or former smoking, total cholesterol, and diabetes.

Results

The study included 10 prospective cohorts totaling 52,674 participants with a median age of 59 years, 58.5% of whom were women. There was a median follow-up of 8.8 years. There were 2188 (4.2%) with suppressed TSH; 1884 (3.6%) had TSH of 0.10 to 0.44 mU/L and 304 (0.6%) had TSH <0.10 mU/L. During follow-up, based on age- and sex-adjusted analyses, the overall hazard ratio (HR) for mortality for subclinical hyperthyroidism as compared with euthyroid participants was 1.24 (95% CI, 1.06 to 1.46). The HR was 1.29 (95% CI, 1.02 to 1.62) for CHD mortality; 1.21 (95% CI, 0.99 to 1.46) for CHD events, and 1.68 (95% CI, 1.16 to 2.43) for incident AF. The HR for CHD mortality was 1.84 (95% CI, 1.12 to 3.00) and for incident AF 2.54 (95% CI, 1.08 to 5.99), which were significantly higher for TSH levels <0.10 mIU/L than those for TSH 0.10 to 0.44 mU/L, but other outcomes did not differ.

Conclusions

Pooled data from prospective cohorts indicates that endogenous subclinical hyperthyroidism is associated with an increased risk of total mortality, CHD mortality, and incident AF, with higher risks of CHD mortality and AF with TSH levels below 0.10 mIU/L.

ANALYSIS AND COMMENTARY

This is the strongest study to date showing that subclinical hyperthyroidism increases mortality, including CHD mortality, in addition to atrial fibrillation. The data confirm the retrospective results of Sawin et al. with regard to atrial fibrillation (1) and the results of Vadiveloo et al. with regard to cardiovascular disease (2), with a TSH level of <0.10 mU/L being more hazardous. The data are at variance with the Cardiovascular Health Study, which reported that SHyper is not associated with other cardiovascular disorders or mortality (3). The reason for this

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is that the current study of over 50,000 participants had more power to show small effects than the study of 2569 subjects in the Cardiovascular Health Study (which was included in the current analysis).

The authors are careful to point out the limitations of the study. One report that was included from Germany had a 24% incidence of SHyper that was attributed to iodine supplementation introduced 4 years earlier, but the results were qualitatively similar when the German report was excluded from the analysis. Another limitation is that the subjects were predominantly white. Although subjects taking thyroid preparations were excluded, not all the studies had data on other medications, such as amiodarone, that could alter thyroid function. Another limitation is that there were only 304 individuals in the group with TSH <0.10 mIU/L, with only 15 deaths in this group.

Although there is still a lack of a randomized controlled study of treatment of SHyper to show that mortality, CHD, and AF can be prevented or reduced, the current study is further ammunition to treat patients with SHyper, especially when the TSH is <0.10 mU/L. In an accompanying invited commentary, Ken Burman reviewed the approach to treatment of these patients (4).

— Jerome M. Hershman, MD

References

1. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'Agostino RB. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994;331:1249-52.
2. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. J Clin Endocrinol Metab 2011;96:1344-51. Epub February 23, 2011.
3. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW. Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 2006;295:1033-41.
4. Burman KD. What is the clinical importance of subclinical hyperthyroidism? Arch Intern Med 2012;172:809-10.

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Focal Thyroid Uptake in Thyroid Incidentalomas Detected by PET Scans Suggests Malignancy

Soelberg KK, Bonnema SJ, Brix TH, Hegedüs L. Risk of malignancy in thyroid incidentalomas detected by (18)F-fluorodeoxyglucose positron emission tomography: a systematic review. Thyroid. July 24, 2012 Jul 24. [Epub ahead of print].

SUMMARY

Background

The use of 18F-fluorodeoxyglucose positron-emission tomography (18F-FDG–PET) scans for screening and follow-up of cancer has increased substantially and has led to detection of lesions in the thyroid gland that were not evident clinically. These lesions have been dubbed "thyroid incidentalomas," and they are found even more commonly by ultrasound as well as by other imaging methods. However, finding them by PET scanning has been considered more ominous because PET scans depend on the uptake of labeled glucose that is based on the fact that malignancies metabolize glucose at a higher rate than normal tissues. In addition, it is known that thyroid malignancies have increased expression of glucose transporters as compared with normal thyroid tissue (1).

The current study is a review of the literature on thyroid incidentalomas found by PET scanning in order to determine the risk of cancer in these lesions.

Methods

The authors searched the PubMed database to find relevant studies, then evaluated 602 abstracts, eventually selecting 22 studies that met their criteria for finding thyroid incidentalomas by PET and that also included follow-up, FNA, or surgery. Studies were excluded if they included participants with a history of thyroid disease or were case reports or evaluated fewer than 10 patients.

Results

Twenty studies were retrospective and 2 were prospective; 11 were performed as part of disease follow-up for staging. All were published before 2010. The total number of subjects was 125,754; the number in each of the 22 studies ranged between 477 and 15,711. Focal thyroid uptake was found in 1994 (1.6%); 1051 had follow-up and 1025 had a diagnosis assigned by cytology or histology. The prevalence of focal uptake varied between 0.1% and 4.8% in the various studies. The prevalence of thyroid cancer in these lesions was 36% and varied from 10 to 64% in different reports. There was a similar mean incidence of malignancy in lesions with focal uptake, about 35%, in studies from the United States, Europe, and Asia. The positive predictive value of focal uptake for malignancy was 39%.

Diffuse thyroid uptake was reported in only eight studies and found in 2.1% of subjects; it varied from 0.1 to 4.4% in different reports. The prevalence of cancer varied from 0 to 13.3% (mean, 3.9%) of those with diffuse uptake, but the diagnosis was established by FNA or histology in only 77 patients. Seven studies did not investigate diffuse uptake because previous reports indicated that diffuse uptake usually represented benign disease, such as chronic thyroiditis or Graves' disease.

In 18 studies, standard uptake values (SUVs) were calculated for the focal uptake, but the manner in which this was done differed among various studies. The SUV expresses the intensity of the uptake. For 80 benign lesions, the mean (±SD) SUV was 4.8±3.1 and for 78 malignant lesions it was 6.9±4.7. Although the means differ significantly, there is considerable overlap.

Conclusions

Thyroid nodules found incidentally using 18F-FDG–PET are at relatively high risk of being malignant if uptake is focal.

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ANALYSIS AND COMMENTARY

The authors have carried out an excellent synthesis of the literature on this topic and have clarified the different diagnostic significance for prediction of malignancy when thyroid uptake in a PET study is focal versus diffuse. Diffuse uptake has poor predictive value for malignancy; in contrast focal uptake suggests malignancy in almost 40% of lesions. However, in this retrospective study, only 29% of the lesions with focal uptake were confirmed by surgery. PET scans are often combined with CT in order to verify that there is an anatomic basis for the labeled glucose uptake, and the CT provides valuable information. Focal uptake without a discernible focal anatomic lesion on CT was indicative of a benign lesion with high certainty (2).

In the early days of PET scanning for indeterminate thyroid nodules, it was hoped that calculation of the SUV, a quantitative value for the intensity of focal uptake, would provide a precise cutoff between malignant and benign lesions, but this has failed to materialize. Nevertheless, there is more concern about malignancy when the SUV is high than when it is low. The SUV has also been found to correlate directly with the size of the lesion (3).

This fact that PET scans showing focal uptake in a thyroid nodule predict malignancy should not be used to promote the use of PET, a very expensive method, for making the diagnosis of cancer in a thyroid nodule. In a study from India comparing PET/CT scans with high-resolution ultrasonography in 200 patients with solitary thyroid nodules, the authors concluded that PET/CT did not have a significant advantage over ultrasonography (4).

— Jerome M. Hershman, MD

References

1. Ciampi R, Vivaldi A, Romei C, Del Guerra A, Salvadori P, Cosci B, Pinchera A, Elisei R. Expression analysis of facilitative glucose transporters (GLUTs) in human thyroid carcinoma cell lines and primary tumors. Mol Cell Endocrinol 2008;291:57-62. Epub May 14, 2008.
2. Choi JY, Lee KS, Kim HJ, Shim YM, Kwon OJ, Park K, Baek CH, Chung JH, Lee KH, Kim BT. Focal thyroid lesions incidentally identified by integrated 18F-FDG PET/CT: clinical significance and improved characterization. J Nucl Med 2006;47:609-15.
3. Bae JS, Chae BJ, Park WC, Kim JS, Kim SH, Jung SS, Song BJ. Incidental thyroid lesions detected by FDG-PET/CT: prevalence and risk of thyroid cancer. World J Surg Oncol 2009;7:63.
4. D'Souza MM, Marwaha RK, Sharma R, Jaimini A, Thomas S, Singh D, Jain M, Bhalla PJ, Tripathi M, Tiwari A, Mishra A, Mondal A, Tripathi RP. Prospective evaluation of solitary thyroid nodule on 18F-FDG PET/CT and high-resolution ultrasonography. Ann Nucl Med 2010;24:345-55. Epub April 7, 2010.

Clinical THYROIDOLOGY
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Metformin Reduces Serum TSH Concentration in Patients with Diabetes

Cappelli C, Rotondi M, Pirola I, Agosti B, Formenti A, Zarra E, Valentini U, Leporati P, Chiovato L, Castellano M. Thyreotropin levels in diabetic patients on metformin treatment. Eur J Endocrinol 2012;167:261-5. Epub May 29, 2012.

SUMMARY

Background

Metformin therapy in patients with diabetes induces a significant lowering in serum TSH concentrations. The objective of this retrospective study was to evaluate changes in TSH concentrations in diabetic patients treated or not treated with metformin and/or L-T_4.

Methods

Three hundred thirty-nine patients with euthyroidism and diabetes were divided into three groups on the basis of metformin and/or L-T_4 treatment. Group (M–/L–): 119 patients never treated with metformin and L-T_4; group (M+/L–): 203 patients who started metformin treatment at recruitment; and group (M+/L+): 71 patients taking L-T_4 who started metformin at recruitment.

Results

The effect of metformin on serum TSH concentrations was analyzed in relation to the basal value of TSH (below 2.5 mIU/L [Group 1] or between 2.51 and 4.5 mIU/L [Group 2]]. In group M+/L+, the mean (±SD) TSH significantly decreased independently from the basal level (Group 1: from 1.45±0.53 to 1.01±1.12 mU/L; P = 0.037; Q2: from 3.60±0.53 to 1.91±0.89 mU/L; P<0.0001). In group M+/L–, the decrease in TSH was significant only in patients with a basal high-normal serum TSH (Group 2: from 3.24±0.51 to 2.27±1.28 mU/L' P = 0.004); in group M–/L–, no significant changes in TSH levels were observed.

In patients of group M+/L–, who showed high-normal basal TSH levels, a significant decrease in TSH was observed independently from the presence or absence of TPOAb (Q2 TPOAb+: from 3.38±0.48 to 1.87±1.08 mU/L; P<0.001; Q2 TPOAb–: from 3.21±0.52 to 2.34±1.31 mU/L; P<0.001).

Conclusions

These data strengthen the known TSH-lowering effect by metformin in patients with diabetes who are undergoing L-T_4 treatment and also show a significant reduction of TSH in euthyroid patients with higher baseline TSH levels independently from the presence of TPOAb.

ANALYSIS AND COMMENTARY

In our daily clinical practice, both hypothyroidism and diabetes mellitus are common diagnoses; metformin therapy is recommended as the first hypoglycemic pharmacologic agent when diabetes type 2 or prediabetes is diagnosed (1). Another indication for metformin is in the treatment of women with polycystic ovary syndrome (PCOS) (2). Type 2 diabetes may develop in patients who are known to have hypothyroidism while undergoing L-T_4therapy, or on the contrary, patients with diabetes mellitus who are undergoing metformin therapy could be diagnosed with hypothyroidism and prescribed L-T_4therapy. In the past few years, several clinical observations have consistently shown a lowering of serum TSH levels in patients with newly diagnosed hypothyroidism or undergoing L-T_4substitution therapy, following the administration of metformin (3,4). In one study, thyroid-function parameters did not change in euthyroid patients with PCOS after starting metformin therapy, but they decreased significantly in patients with hypothyroidism and PCOS after a 4-month course of metformin treatment, from the basal median serum

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levels of TSH (3.2 mIU/L [range, 0.4 to 7.1 mIU/L] to 1.7 mIU/L [range, 0.5 to 5.2 mIU/L]); as in other studies, no significant change in the serum levels of FT_4 was observed (5). In addition, the TSH-lowering effect of metformin was not related to the dose of the drug administered. The study by Cappelli et al. included three groups of patients with diabetes, confirming previous published observations of decreased serum TSH levels in patients with hypothyroidism who were undergoing L-T_4 treatment after metformin therapy; the two new interesting findings were that in patients with metformin-treated diabetes and who were not undergoing L-T_4 therapy, the decrease in TSH levels was significant only in the patients with a high-normal basal serum TSH (between 2.5 and 5 mIU/L)— from 3.24±0.51 to 2.27±1.28 mU/L (P = 0.004). In contrast, TSH significantly decreased independently from the basal level in patients undergoing L-T_4 therapy. The second finding of interest is that the effect of metformin appears to occur independently of the presence or absence of TPOAb.

At the moment, the mechanisms by which metformin would exert its TSH-lowering effect remain not fully elucidated. The two emerging hypothesis to explain the effect of metformin on TSH involves the action of metformin on 5′ adenosine monophosphate–activated protein kinase (AMPK) (6) and the central effect of metformin mediated by a reduction of circulating fatty acids (7).

What is the clinical impact of these observations on the care of our patients with diabetes and/or hypothyroidism? Since a vast majority of our patients with both disorders are at higher risk for other cardiovascular risk factors, a careful assessment of thyroid function to prevent the development of subclinical hyperthyroidism is highly recommended in patients with untreated subclinical hypothyroidism and in those undergoing L-T_4 therapy when metformin is added to their therapeutic regimen.

— Jorge H. Mestman, MD

References

1. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364-79. Epub April 19, 2012.
2. Dunaif A. Drug insight: insulin-sensitizing drugs in the treatment of polycystic ovary syndrome—a reappraisal. Nat Clin Pract Endocrinol Metab 2008;4, 272-83. Epub March 25, 2008.
3 Vigersky RA, Filmore-Nassar A, Glass AR. Thyrotropin suppression by metformin. J Clin Endocrinol Metab 2006;91:225-7. Epub October 11, 2005.
4. Cappelli C, Rotondi M, Pirola I, Agosti B, Gandossi E, Valentini U, De Martino E, Cimino A, Agabiti Rosei E, Castellano M. TSH-lowering effect of metformin in type 2 diabetic patients. Diabetes Care 2009;32:1589-90. Epub June 5, 2009.
5. Rotondi M, Cappelli C, Magri F, Botta R, Dionisio R, Iacobello C, De Cata P, Nappi RE, Castellano M. Chiovato L. Thyroidal effect of metformin treatment in patients with polycystic ovary syndrome. Clin Endocrinol 2011;75:378-81.
6. Duntas LH, Orgiazzi J, Brabant G. The interface between thyroid and diabetes mellitus. Clin Endocrinol. February 24, 2011 [Epub ahead of print].
7. López M, Varela L, Vázquez MJ, et al. Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. Nat Med 2010;16:1001-8. Epub August 29, 2010.

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T_3 Stimulates Hepatic Fatty Acid β–Oxidation by Inducing Lipophagy

Sinha RA, You SH, Zhou J, Siddique MM, Bay BH, Zhu X, Privalsky ML, Cheng SY, Stevens RD, Summers SA, Newgard CB, Lazar MA, Yen PM. Thyroid hormone stimulates hepatic lipid catabolism via activation of autophagy. J Clin Invest 2012;122:2428-38. Epub June 11, 2012.

SUMMARY

Background

In the liver, physiological mobilization and metabolism of free fatty acids is a crucial step in intracellular energy transfer. Autophagy is an essential cellular degradation process of proteins and organelles. Recently, it was shown that autophagy is also involved in the transfer of lipid droplets to mitochondria—a process termed "lipophagy." It is probably a major pathway of lipid mobilization. For more than 100 years, thyroid hormones were known to stimulate basal metabolic rate. Several hypotheses have been proposed to explain the mechanisms underlying this phenomenon. Yet, a satisfactory explanation is still missing. The authors of the present article provide important new information by demonstrating that the induction of lipophagy is under the control of thyroid hormones.

Methods and Results

In vitro studies were performed with hepatic cell cultures (HepG2 cells) transfected with functional T_3 receptors. In the present studies, an easily identifiable form of LC3 (i.e., LC3 conjugated to phosphatidylethanolamine (LC3-II) was studied. LC3-II is a critical component of autophagosomes. An increase in LC3-II indicates increased autophagy and is the most common marker of autophagy. Low concentrations of T_3, similar to those encountered in vivo, are able to stimulate synthesis of LC3. More refined studies indicated that autophagic clearance was simultaneously increased, and therefore the net LC3-II production was even greater. In further studies, the authors confirmed increased autophagosomes and lipophagy by using fluorescence techniques and electron microscopy. Morphologic evidence confirmed the increased number of autophagosomes and lipophagosomes within autolysosomes and lipid droplets. Using a knockin mouse model expressing a mutant T_3 receptor known to confer resistance to thyroid hormone, the authors elegantly demonstrated that T_3-mediated autophagy required a fully functional T_3 receptor. In addition, they showed that lipophagy is tightly coupled with β-oxidation. Metabolomic analysis confirmed that there was an increased flux of fatty acid metabolites in the liver of T_3-treated mice as compared with mice with hypothyroidism.

Conclusions

One of the mechanisms whereby thyroid hormones participate in the control of energy expenditure is the activation of β-oxidation of fatty acids. The present finding that T_3 is specifically promoting lipophagy is consistent with its key role as an important regulator of the delivery of fatty acids to mitochondria. The data provide support for a novel mechanism that increases fat energy expenditure.

ANALYSIS AND COMMENTARY

Practicing physicians are often confronted with questions from patients concerning the mechanism of thyroid hormone action. The standard answer is an increase in metabolic rate or, in other words, of oxygen consumption in a quiet state. This remains a very elusive answer. Increased metabolic rate during hyperthyroidism requires mobilization of lipids and carbohydrates. For instance, the muscle glycogen stores are rapidly depleted. In this article, we find an answer to the question of how increased hepatic lipid oxidation is controlled by thyroid hormones. This is certainly a remarkable addition to our knowledge, even though it is only one piece of a puzzle.

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Autophagy is a complex mechanism that is regulated by insulin and glucagon in the liver; however, their role in lipophagy is not known. So far, only T_3 has been shown to regulate lipophagy and thereby provide substrate for hepatic mitochondrial β-oxidation of fatty acids. T_3 is decreased not only in hypothyroidism but also during fasting and during the euthyroid sick syndrome, and it has been shown that the hypothyroid liver is more sensitive to fatty degeneration (1). The new discovery of T_3-regulated lipophagy raises many questions that will stimulate clinical research.

Albert G. Burger MD

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REFERENCE

1. Chung GE, Kim D, Kim W, Yim JY, Park MJ, Kim YJ, Yoon JH, Lee HS. Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. J Hepatol 2012. 57:150-6. Epub March 14, 2012.

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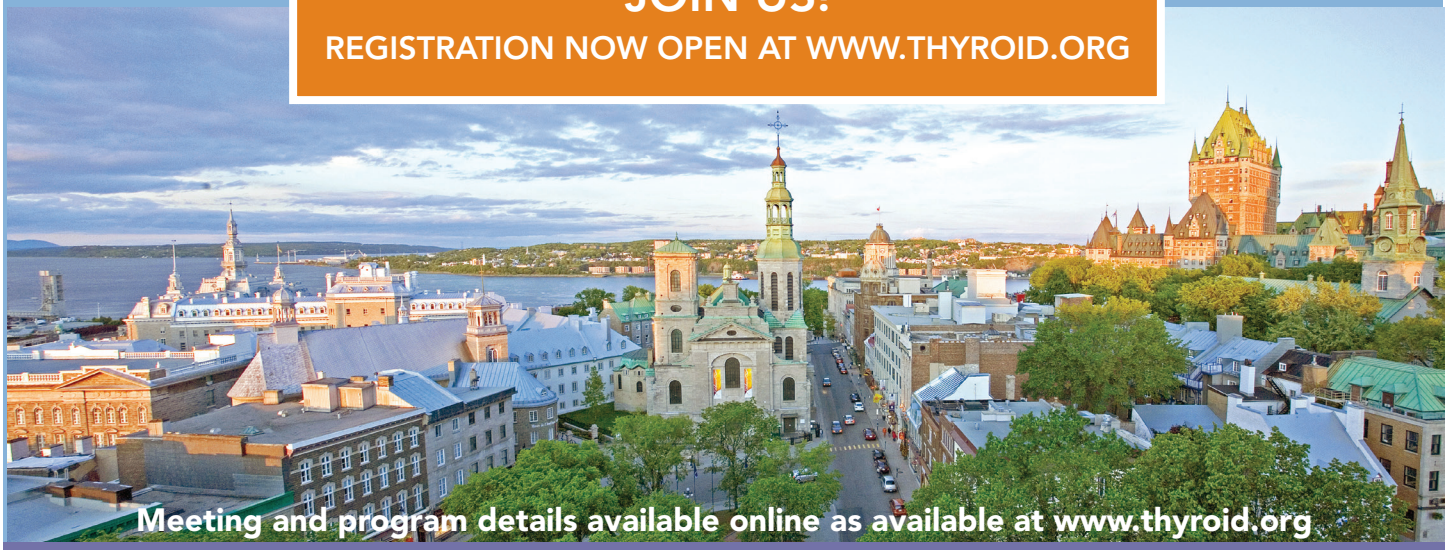

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