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Which Contributes More to the Increased Mortality in Hyperthyroidism: The Type of Therapy or Prolonged Incomplete Control of Hyperthyroidism?

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SUMMARY

Background

Several studies have indicated that patients with hyperthyroidism who are treated with ^{131}I are at increased risk of morbidity and mortality, as compared with a general population (1,2). The current paper tries to address some related questions, such as: 1) Do patients treated with antithyroid drugs (ATDs) also have an increased risk of mortality? 2) Does the length of time a patient remains hyperthyroid or subclinically hyperthyroid have an effect on mortality? 3) Do preceding comorbid conditions increase the risk of mortality? and 4) Does the increased risk occur shortly after treatment or does it persist after a long follow-up time?

Methods

The authors reviewed records on 2389 patients with hyperthyroidism who were initially evaluated between 1989 and May 31, 2003, at the Birmingham thyroid clinic and who had been followed for at least 10 years or else had died. After excluding 1353 patients for being under 40 years of age, having had been treated previously, having transient thyroiditis, having received amiodarone, having emigrated, or being lost to follow-up, 1036 were left for the study. Patients were deemed to have Graves' disease if at least two of the following had been present: a palpable diffuse goiter, a positive TPO and/or Tg antibody titer, or thyroid eye disease (345 patients). Patients with a palpable nodular goiter were deemed to have toxic nodular goiter (TNG, 285 patients). The etiology for the remaining 406 patients was deemed indeterminate, but most would have had either Graves' or toxic nodular disease. No information about thyroid imaging, TSH-receptor antibody levels or cardiovascular medications (other than the exclusion of those on amiodarone) was provided.

All patients were either given ATDs or ^{131}I. Patients with Graves' disease received ATDs 2.5 times more often than those with TNG. Of the 376 patients initially started on ATD treatment, 90% received carbimazole (maintenance dose, 5 to 10 mg/day) and 10% received propylthiouracil (PTU) (maintenance dose, 50 to 100 mg/day). Patients were seen in follow-up at least every 2 months until their hyperthyroidism was controlled (free T_4, <20 pmol/L). Of those initially given ATDs, 104 (28%), including more severe cases and elderly patients, were given ^{131}I after about 2 months of ATDs. Of those who were taking only ATDs after 12 to 18 months, 52% had gone into remission, while the remaining 20% had hyperthyroidism but continued taking ATDs. ATDs were withheld for at least a week before and after giving one or more fixed doses of ^{131}I. The fixed dose was generally 5 mCi before 1995, 10 mCi from 1995 to 2000, and 16 mCi from 2001 to 2003.

Patient-years of treatment were divided into three phases: first, the number of years a patient remained on ATD therapy or remained in remission after having taken only ATD; second, the years after taking ^{131}I that a patient went without needing to take L-T_4; and third, the number of years after taking ^{131}I that a patient received L-T_4. A patient's treatment years could have included all three phases, but death was ascribed to the last phase entered.

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Preceding comorbidities were determined by looking at patient records. A patient's cause of death was based on the International Classification of Diseases, revision 9 (ICD-9) or ICD-10 code given on the death certificate. Mortality rates were compared between the patient-years spent in the three phases, and also compared to the mortality rate in the general population in England and Wales, adjusted for sex, age, and period of study. Multiple statistical approaches were used, including multivariable Cox proportional-hazards regression models to assess the influence of different treatment groups, causes of hyperthyroidism, disease severity (initial level of free T_3 and/or T_4), disease control (serial free T_4 levels), preceding comorbidity, and period of enrollment (pre-1995, 1995 to 2000, and 2001 to 2004 [sic]).

Results

During 12,868 years of patient follow-up, 334 died—15% more than projected based on standardized mortality in the general population (P = 0.01). The risk was increased by more than 50% in those with preceding comorbidity, in those who presented with atrial fibrillation, and in current smokers. Of note, no increase in mortality was observed in the first year of follow-up, whereas increased mortality was consistently found after more than 10 years of follow-up (P<0.05). Of the "excess" deaths, half were "circulatory deaths," which is 20% more than expected (P<0.05).

During the 3325 patient-years during which patients took only ATDs or were in remission after ATD therapy, there were 88 deaths, which was 30% more than all-cause mortality in the control population (P<0.02). During the 3045 patient-years during which patients did not require L-T_4 after receiving ^{131}I, all-cause mortality was almost 25% greater than in the control population (P<0.01). During the 6498 patient-years during which patients needed L-T_4 after getting ^{131}I, however, the overall mortality was not increased as compared with the control population. When mortality in the total cohort of 1036 patients was subjected to multivariable analysis, the group that underwent ^{131}I treatment and then needed L-T_4 actually had significantly lower mortality rates than either those who only took ATDs (30%) or those who took ^{131}I but did not require L-T_4 (25%). An analysis of patients with preceding comorbidity, and an analysis of the combined subgroup of patients with Graves' and TNG, however, did not show a significant reduction in risk of mortality in those taking L-T_4 after receiving ^{131}I.

The percentage of patients who were given ^{131}I but in whom hypothyroidism did not develop rose with patient age, whereas the percentage of patients in whom hypothyroidism developed and required L-T_4 decreased with age. Patients with TNG and those with preceding comorbidities were also less likely to have hypothyroidism after ^{131}I. Supplementary graphs displaying serial free T_4 levels in all patients over 5 years of follow-up revealed that many of the 492 patents who needed to take L-T_4 had free T_4 levels substantially below 9 pmol/L over the 6-month period after receiving ^{131}I. In contrast, 20% of the 272 patients who had taken only ATDs still had a suppressed TSH at 1 year, while 12.8% of the 764 given ^{131}I still had an undetectable TSH 1 year after the first dose, indicating that subclinical hyperthyroidism persisted in a substantial fraction of those given either treatment. Mortality increased if a patient's free T_4 rose by 10 pmol/L during the serial measurements. Unfortunately, no supplementary graphs of the patients' serial TSH values were provided.

Conclusions

In the cohort of 1036 patients with hyperthyroidism who were followed for at least 10 years, 15% more died than would have been expected in the general population. A patient's risk of mortality increased by more than 50% if he or she smoked, had preceding comorbidities, or had atrial fibrillation. The authors found mortality to be increased in those treated with ATDs alone, and confirmed their previous report that mortality was increased in those who did not need to take L-T_4 after receiving ^{131}I, while in contrast, mortality was not increased in those in whom hypothyroidism developed after receiving ^{131}I but then needed to take L-T_4. Mortality in that group was 25% to 30% lower than in the other two groups.

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ANALYSIS AND COMMENTARY

The finding that patients with hyperthyroidism who had been treated only with ATDs are at increased risk of mortality is certainly provocative and should stimulate others to organize more focused prospective studies. The authors needed to combine cases seen over a 15-year period, which may have exposed their study to shifting baselines. For example, over the period of the study, the Birmingham group changed the way they used ^{131}I, using an ablative dose in the most recent period. In addition, over the period of the study, diagnostic tests (e.g., various thyroid scans, TSH, and TSI/TRAb assays), exacerbating factors (e.g., smoking), and treatments for comorbid conditions associated with hyperthyroidism also improved, and indeed death certificates citing hyperthyroidism as the cause of death, as well as those with any mention of hyperthyroidism declined in the United Kingdom, as recently discussed (3). Nonetheless, the decline in mortality assessed over the three treatment periods for the total cohort did not turn out to be significant.

Up to 1995, the Birmingham group used a fixed dose of 5 mCi of ^{131}I in hopes of reducing the incidence of hypothyroidism, but they found that 34% of patients with TNG and 56% of those with Graves' disease continued to have hyperthyroidism at 6 months (4). In the current paper, they found that the risk of mortality increased significantly (P = 0.009) if the free T_4 level rose 10 pmol/L on the serial free T_4 measurements during treatment. These findings emphasize the importance of prompt, close control of hyperthyroidism.

Another factor that may have influenced the results is that some patients were taking ATDs up to a week before of the administration of 5 mCi of ^{131}I, which Allahabadia et al. showed to be a significant predictor of failure to respond to ^{131}I (5). There is also some evidence suggesting that ATDs may affect the response of TNG glands to ^{131}I differently from the response of Graves' glands (reviewed in 6).

ATDs were used much less frequently in patients with TNG, whereas ^{131}I was used more frequently in patients with TNG than in patients with Graves' disease. The patients who did not require L-T_4 after receiving ^{131}I obviously maintained a higher level of T_4, and thus presumably were more likely to be in the group with subclinical hyperthyroidism after 1 year. The percentage of patients given ^{131}I in whom hypothyroidism did not develop rose progressively with patient age, whereas the percentage in those in whom hypothyroidism did develop and who required L-T_4 fell progressively with patient age. Furthermore, of all those given ^{131}I, more than 80% of patients with Graves' disease required L-T_4, whereas only 46% of those with TNG required L-T_4. What is more, patients with TNG and those with preceding comorbidities were also less likely to have hypothyroidism after ^{131}I therapy. All these factors could be involved in the reduced mortality observed in those in whom hypothyroidism developed and who needed L-T_4 after receiving ^{131}I.

Supplementary graphs displaying serial free T_4 levels in all patients over 5 years of follow-up showed that many of the 492 patents who needed to take L-T_4 had free T_4 levels substantially below 9 pmol/L over the 6 months after receiving ^{131}I. One might speculate that this period of hypothyroidism—although probably bad for Graves' orbitopathy—was less hazardous in terms of mortality than the persistence of subclinical hyperthyroidism in some patients who did not need L-T_4 after receiving ^{131}I, and also in some of those treated only with ATDs.

In 1998, the authors reported that ^{131}I treatment was associated with a higher mortality, as compared with the general population (2). In 2005, they first reported increased mortality in patients treated with ^{131}I who did not require L-T_4, and that excess mortality was not found in those in whom hypothyroidism developed and who required L-T_4 after ^{131}I (7); that paper studied patients enrolled from 1984

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through 2002, so presumably data from some of the same patients were also included in the current paper. In the current paper, the increased risk of mortality was most clear-cut after more than 10 years of follow-up. This is in striking contrast to the authors' earlier report that excess mortality was most prominent in the first year after ^{131}I and declined thereafter (2). Indeed, Metso et al. reported that the increased risk of cardiovascular morbidity persists for up to 35 years after ^{131}I administration (1).

Atrial fibrillation clearly is an important factor in the increased risk of mortality in Graves' disease, and it should also be noted that atrial fibrillation increases long-term mortality by 50% in the general euthyroid population as well. An interesting recent nationwide survey from Denmark found that new-onset atrial fibrillation actually is predictive of the later development of hyperthyroidism (8). The same group recently presented an abstract on a nationwide survey of overall cardiovascular mortality in individuals with a normal free T_4 who were followed for up to 10 years: there was a progressive increase in mortality in those whose TSH was <0.1 (24% increased risk), in those whose TSH was between 0.1 and 0.2 mU/L (21% increased risk), and in those whose TSH was between 0.2 and 0.4 mU/L (21% increased risk) (9).

There could be a problem with trying to apply the current findings to the average case of hyperthyroidism, because patients under 40 were excluded, thus altering the sex-distribution and etiologies seen in the general population. Nonetheless, the findings do make one possible therapeutic intervention stand out: convincing a patient with hyperthyroidism to stop smoking could reduce his or her risk of premature death. This study should prompt the development of larger time-limited prospective studies that include more advanced tests that focus on cases with well-defined etiologies of hyperthyroidism and that address specific factors suspected of being involved in the increased mortality of subgroups of patients, such as those with other autoimmune conditions (including antibodies to cardiac antigens), those with single-nucleotide polymorphisms believed to increase the risk of atrial fibrillation and of thrombosis, those taking specific cardiac medications, and other factors as well.

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