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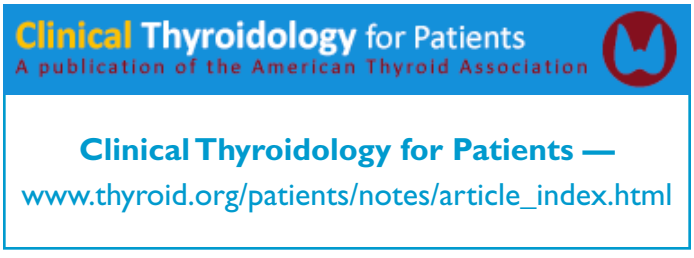

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EDITOR'S COMMENTS

This is the fifth 2009 issue of *Clinical Thyroidology*. As you may know, each issue will be sent to you by email as a separate list of articles that can be downloaded individually or as the entire document.

We wish to thank Drs. Sarah Danzi, and Irwin Klein, for their CONCISE REVIEW on alterations in thyroid Hormones and cardiovascular disease in this issue of *Clinical Thyroidology*.

FIGURES You will notice that the articles in *Clinical Thyroidology* contain figures with the ATA logo and a citation with the volume and issue numbers. We encourage you to continue using these figures in your lectures, which we hope will be useful to you and your students.

WHATS NEW The last page now has a set of references to REVIEWS & HOT ARTICLES which contains references to important reviews and very recent articles that look especially important to the Editors.

EDITOR'S CHOICE ARTICLES are particularly important studies that we recommend you read in entirety.

We welcome your feedback and suggestions on these changes.

CONCISE REVIEW CITATIONS: Beginning with the first review article for *Clinical Thyroidology* by Dr. Elaine Ron, authors can cite our CONCISE REVIEWS by using the electronic citation at the end of each review.

Ernest L. Mazzaferri, MD, MACP
Jennifer A. Sipos, MD

How to navigate this document: The Table of Contents and the Bookmarks are linked to the articles. To navigate, move your cursor over the article title you wish to see (either in the Contents or in the Bookmarks panel) and the hand will show a pointing finger, indicating a link. Left-click the title and the article will instantly appear on your screen. To return to the Contents, move the cursor to the bottom of the page and left-click Back to Contents which appears on every page. If you would like more information about using Bookmarks please see the help feature on the menu bar of Acrobat Reader.

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Alterations in thyroid hormones that accompany cardiovascular disease

Some of the most characteristic signs and symptoms of thyroid disease are those resulting from the effects of thyroid hormone on the heart and cardiovascular system. Many published reports have noted that the clinical findings resulting from excess thyroid hormone are more pronounced and prevalent than those resulting from thyroid hormone deficiency. Thus palpitations and tachycardia are reported in the majority of patients with hyperthyroidism whereas in hypothyroidism, the decrease in exercise tolerance, rise in diastolic blood pressure and decreases in cardiac contractility are much more subtle findings.

Thyroid hormone affects almost every tissue and organ system in the body, regulating basal metabolism and tissue thermogenesis (1; 2). Hyperthyroidism, either exogenous (resulting from over treatment) or endogenous (usually Graves' disease) causes predictable changes in cardiovascular hemodynamics (3). Excess thyroid hormone leads to predictable decreases in systemic vascular resistance (SVR) and increases in resting heart rate, left ventricular ejection fraction, cardiac contractility and mass, blood volume and cardiac output. The increased systolic, and decreased diastolic, blood pressure causes a widened pulse pressure. The symptoms of exercise intolerance and dyspnea are due to an inability to further increase heart rate or ejection fraction or further lower SVR in response to increased muscular work. In addition, respiratory and skeletal muscle weakness as well as a rise in pulmonary artery pressure can impair maximum exercise capacity. The reduction in SVR is mediated by a direct effect on vascular smooth muscle in peripheral arterioles which decreases mean arterial pressure. Blood volume is increased through activation of the renin-angiotensin-aldosterone system and increased renal sodium absorption. Triiodothyronine (T_3) also increases erythropoietin synthesis, which leads to an increase in red cell mass. Together, these changes increase blood volume and preload. Cardiac output may increase by 50% to 300%. The rate of left ventricular (LV) relaxation (as measured by isovolumic relaxation time), and LV filling are enhanced by the effects of thyroid hormone. LV hypertrophy results from sustained volume overload and the resulting increase in cardiac work load.

The effects of hypothyroidism are diametrically opposite to those of hyperthyroidism. Patients with the former have decreased cardiac output, bradycardia, narrowed pulse pressure and mild hypertension with increased SVR with decreased ventricular filling and diastolic relaxation. Symptoms are not specific and include fatigue, weight gain and cold intolerance, all of which are reversible with thyroid hormone replacement. Hypothyroidism is characterized by hypercholesterolemia and a marked increase in low-density lipoproteins (LDL) and apolipoprotein B due to alterations in lipid metabolism. Therefore, hypothyroid patients have increased risk of cardiovascular disease and an apparent increase in risk of stroke as well.

The cellular mechanisms of thyroid hormone action are mediated by nuclear thyroid hormone receptor proteins which regulate the transcription of many important genes. Thyroid hormone receptors belong to the superfamily of steroid receptors but are unique in that they are bound to response elements in the promoter regions of target genes in the absence as well as presence of T_3, unlike steroid receptors which are anchored in the cytoplasm until they bind their specific ligands. The transport of thyroid hormone into cells has been the topic of much recent investigation. Unlike many cell types including the liver, pituitary and skeletal muscle, it appears that the cardiac myocyte transports T_3 in marked preference to T_4 (4). In recent studies from our laboratory, T_3 and not T_4 is transcriptionally active in regulating the expression of important myocyte genes (5). Thus in the presence of normal serum T_4, but low serum T_3, there are alterations in cardiac gene expression which are similar to that of primary hypothyroidism as well as chronic congestive heart failure (HF). In the heart, T_3 target genes include those whose expression is also altered in heart failure as will be discussed below.

The thyroid gland produces primarily thyroxine (T_4) and to a lesser degree, T_3. The majority of serum T_3 is derived from 5'-monodeiodination either in the kidney and liver (D1) or from skeletal muscle (D2). A variety of factors including proinflammatory cytokines have been identified which impair the ability of the deiodinase enzyme system to metabolize T_4 which leads to decreased serum T_3 content (6). Previously this group of conditions was referred to as the sick euthyroid syndrome however, in light of recent evidence, the term low T_3 syndrome or nonthyroidal illness appears to be more appropriate. This conclusion derives from the fact that in many of these acute and chronic illnesses low T_3 levels may result in physiologic impairment questioning the appropriateness of the term "euthyroid."

Dating back to the first observations by Hamilton and colleagues (7), it has been shown that altered T_4 metabolism occurs in patients with HF. In almost all cases, the low serum T_3 levels are accompanied by normal thyroid stimulating hormone (TSH) and T_4. In Table 1 we have reviewed the variety of cardiac disease states that have been reported to alter thyroid hormone metabolism. This list has recently been expanded to include the unique group of patients with stress cardiomyopathy as reported by Lee et al. (8) and reviewed in this issue of Clinical Thyroidology. While their careful description of these changes in thyroid hormone metabolism are of interest, it begs the question as has been raised with other cardiac disease states, of whether thyroid hormone replacement, specifically T_3, can be a useful and novel treatment modality to facilitate improvement and recovery of cardiac function in these patients.

Table 1. Cardiovascular disease states that alter thyroid hormone metabolism

- Acute myocardial infarction
- Acute viral myocarditis
- Stress cardiomyopathy
- Heart failure – in proportion to the degree of severity
- Coronary artery bypass surgery
- Congenital heart disease surgery
- Amiodarone treatment (not dronedarone)

Table 2. Similarities between hypothyroidism and heart failure

Characteristics	Hypothyroidism	HF
Cardiac output	↓	↓
Cardiac contractility	↓	↓
Serum T_3 levels	↓	↓
Ischemic heart disease	±	+++
Systemic vascular resistance	↑	↑
Response to thyroid hormone	+++	?

Table 3. Potential benefits of T_3 treatment in heart failure

- Restore serum T_3 to normal
- Improve skeletal muscle function
- Positive lusitropic agent
- Antiarrhythmic effect on QT interval
- Decrease systemic vascular resistance
- Promote reverse remodeling
- Oxygen cost of T_3-mediated increases in cardiac work less than standard cardiac active agents

To date, the evidence that T_3 treatment can be of benefit in nonthyroidal illness in the setting of cardiac disease has arisen in a number of studies. These include the early reports that iv T_3 infusion can improve cardiac output in patients with New York Heart Association Class III-IV HF and in patients with low ejection fraction after undergoing coronary artery bypass grafting. Children undergoing surgery to repair congenital cardiac defects also benefit from the restoration of low serum T_3 levels to normal via infusion of iv T_3 in the 24-72 hours postoperative period.

Thyroid hormone metabolism is altered in patients with HF or following acute myocardial infarction resulting in the low T_3 syndrome (Table 1) (9-11). In addition to potential alterations in D1 and D2, the type 3 deiodinase converts T_4 and T_3 to the inactive compounds reverse T_3 (rT_3) and diiodothyronine (T_2) respectively and a recent study reported that cardiac D3 activity was induced in the infarcted and pathologically hypertrophic myocardium in experimental animals (12-14). In patients with HF, the decrease in serum T_3 concentration is proportional to the severity of the heart disease as assessed by the New York Heart Association (NYHA) functional classification and has been shown to be the most powerful predictor of all cause and cardiac mortality in patients with cardiac disease (7; 11; 15; 16). Cardiopulmonary bypass surgery causes an induction of proinflammatory cytokines such as interleukin-6, and an acute reduction in serum T_3 levels in children and adults (10; 17; 18). Often misunderstood, T_3 administration does not impair cardiac metabolic efficiency because the increase in cardiac output is offset by the decrease in SVR and afterload. The net effect is to enhance cardiac performance without an untoward increase in oxygen demand. T_3 improves the ratio of cardiac work to myocardial oxygen consumption, a reliable measure of myocardial efficiency (19).

T_3 regulates cardiac function as well as SVR through a combination of genomic and nongenomic mechanisms. T_3 controls cardiac contractility and relaxation via multiple mechanisms including the regulation of genes in the cardiac myocyte, specifically those genes encoding the contractile proteins, α- and β-myosin heavy chain (MHC), the sodium calcium exchanger (NCX1) and the sarcoplasmic reticulum calcium activated ATPase (SERCA2). In the failing human heart, α-MHC and SERCA2 are decreased while β-MHC expression is increased (20-22). These genes are positively and negatively regulated by thyroid hormone respectively (3). The SERCA2 pump actively transports and sequesters calcium in the sarcoplasmic reticulum during diastole. Active myocardial relaxation is a function of diastolic intracellular calcium levels and the detachment of myosin heads from actin filaments which enables the sarcomeres to lengthen. Thyroid hormone induces the expression of SERCA2 and the fast myosin heavy chain isoform. Together the enhanced expression of these proteins is largely responsible for enhanced contractile function and diastolic relaxation mediated by thyroid hormone (23). In fact, the list of important cardiac genes that are altered in HF is strikingly similar to the list of genes that are altered in hypothyroidism (Table 2). Since the hypothyroid myocardium responds in a predictable manner to thyroid hormone replacement (24-26) the recent studies in both animals and man to establish a safe and effective role for T_3 replacement in a physiologic manner seems well justified. Interestingly, death from heart disease and HF usually occurs as a result of cardiac arrhythmia and in fact, the most common electrocardiographic changes associated with hypothyroidism are sinus bradycardia and a prolonged QT interval. The latter in turn predisposes to increased ventricular irritability and ventricular tachycardia. Together, this suggests that low T_3 syndrome may also contribute to the risk of death from cardiac arrhythmias in patients with heart disease and low serum T_3 levels and supports the hypothesis that T_3 treatment of heart failure with the low T_3 syndrome can provide additional beneficial effects (Table 3).

Amiodarone is a benzofuran derived Class III anti-arrhythmic that contains 30% iodine by weight. It is frequently used for the treatment of atrial fibrillation, despite the fact that it is only approved for the treatment of ventricular tachyarrhythmias. Soon after introduction it was observed that amiodarone produced predictable changes in thyroid hormone levels including decreases in serum T_3, mild and overt primary hypothyroidism and occasionally thyrotoxicosis. While it has been presumed that these effects were the result of the excess iodine load, only the recent studies with dronedarone, the iodine free congener which produces little if any alterations in thyroid function have confirmed this suspicion.

In Summary, thyroid hormone plays a critical role in the regulation of cardiac function and cardiovascular hemodynamics. The reduction in physiologic serum T_3 that occurs in HF and other cardiovascular disease states potentially further impairs cardiac function in an already compromised heart suggesting that T_3 replacement therapy may benefit patients with low T_3 syndrome.

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References

1. Silva JE. Thermogenic mechanisms and their hormonal regulation. Physiol Rev. 2006, 86:435-64.

2. Bianco AC, Maia AL, da Silva WS, Christoffolete MA. Adaptive activation of thyroid hormone and energy expenditure. Biosci Rep. 2005, 25:191-208.

3. Klein I, Danzi S: Thyroid Disease and the Heart. Circulation, 116: 1725-1735, 2007.

4. Everts ME, Verhoeven FA, Bezstarosti K, Moerings EP, Hennemann G, Visser TJ, Lamers JM. Uptake of thyroid hormones in neonatal rat cardiac myocytes. Endocrinology. 1996, 137:4235-42.

5. Danzi S, Klein I. T_3 and not T_4 regulates gene expression in the mammalian myocyte. Abstract, 79th Annual Meeting of the American Thyroid Association, Chicago. Thyroid. 2008, 18:S1:S83.

6. Boelen A, Maas MA, Lowik CW, Platvoet MC, Wiersinga WM. Induced illness in interleukin-6 (IL-6) knock-out mice: a causal role of IL-6 in the development of the low 3,5,3'-triiodothyronine syndrome. Endocrinology. 1996, 137:5250-4.

7. Hamilton MA, Stevenson LW, Luu M, Walden JA. Altered thyroid hormone metabolism in advanced heart failure. J Am Coll Cardiol. 1990, 16:91-5.

8. Lee SJ, Kang JG, Ryu OH, Kim CS, Ihm SH, Choi MG, Yoo HJ, Hong KS. The relationship of thyroid hormone status with myocardial function in stress cardiomyopathy. Eur J Endocrinol 2009, 160:799-806.

9. Franklyn JA, Gammage MD, Ramsden DB, Sheppard MC. Thyroid status in patients after acute myocardial infarction. Clin Sci (Lond). 1984, 67:585-90.

10. Klemperer JD, Klein I, Gomez M, Helm RE, Ojamaa K, Thomas SJ, Isom OW, Krieger K. Thyroid hormone treatment after coronary-artery bypass surgery. N Engl J Med. 1995, 333:1522-7.

11. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A, Donato L. Low-T_3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation. 2003, 107:708-13.

12. Olivares EL, Marassi MP, Fortunato RS, da Silva AC, Costa-e-Sousa RH, Araújo IG, Mattos EC, Masuda MO, Mulcahey MA, Huang SA, Bianco AC, Carvalho DP. Thyroid function disturbance and type 3 iodothyronine deiodinase induction after myocardial infarction in rats a time course study. Endocrinology. 2007, 148:4786-92.

13. Bianco AC, Larsen PR. Cellular and structural biology of the deiodinases. Thyroid. 2005, 15:777-86.

14. Pol CJ, Muller A, Simonides WS. Cardiomyocyte-specific inactivation of thyroid hormone in pathologic ventricular hypertrophy: an adaptive response or part of the problem? Heart Fail Rev 2008, 10.1007/s10741-008-9133-712-24-2008 [doi]

15. Ascheim DD, Hryniewicz K. Thyroid hormone metabolism in patients with congestive heart failure: the low triiodothyronine state. Thyroid 2002, 12:511-15.

16. Pingitore A, Landi P, Taddei MC, Ripoli A, L'Abbate A, Iervasi G. Triiodothyronine levels for risk stratification of patients with chronic heart failure. Am J Med. 2005, 118:132-6.

17. Chowdhury D, Ojamaa K, Parnell VA, McMahon C, Sison CP, Klein I: A prospective randomized clinical study of thyroid hormone treatment after surgery for complex congenital heart disease. J Thorac CV Surg 2001, 122:1023-25.

18. McMahon CK, Klein I, Ojamaa K: Interleukin-6 and Thyroid Hormone Metabolism in Pediatric Cardiac Surgery Patients. Thyroid 2003, 13: 301-4.

19. Bengel FM, Nekolla SG, Ibrahim T, Weniger C, Ziegler SI, Schwaiger M. Effect of thyroid hormones on cardiac function, geometry, and oxidative metabolism assessed noninvasively by positron emission tomography and magnetic resonance imaging. J Clin Endocrinol Metab. 2000, 85:1822-7.

20. Miyata S, Minobe W, Bristow MR, Leinwand LA. Myosin heavy chain isoform expression in the failing and nonfailing human heart. Circ Res. 2000, 86:386-90.

21. Nakao K, Minobe W, Roden R, Bristow MR, Leinwand LA. Myosin heavy chain gene expression in human heart failure. J Clin Invest. 1997, 100:2362-70.

22. Lowes BD, Minobe W, Abraham WT, Rizeq MN, Bohlmeyer TJ, Quaife RA, Roden RL, Dutcher DL, Robertson AD, Voelkel NF, Badesch DB, Groves BM, Gilbert EM, Bristow MR. Changes in gene expression in the intact human heart. Downregulation of alpha-myosin heavy chain in hypertrophied, failing ventricular myocardium. J Clin Invest. 1997, 100: 2315-24.

23. Mintz G, Pizzarello R and Klein I: Enhanced left ventricular diastolic function in hyperthyroidism: Noninvasive assessment and response to treatment. J Clin Endo Metab 1991, 73:146-50.

24. Ladenson PW, Sherman SI, Baughman KL, Ray PE, Feldman AM. Reversible alterations in myocardial gene expression in a young man with dilated cardiomyopathy and hypothyroidism. Proc Natl Acad Sci U S A. 1992, 89:5251-5.

25. Crowley WF Jr, Ridgway EC, Bough EW, Francis GS, Daniels GH, Kourides IA, Myers GS, Maloof F. Noninvasive evaluation of cardiac function in hypothyroidism. Response to gradual thyroxine replacement. N Engl J Med. 1977, 296:1-6.

26. Klein I: Endocrine disorders and cardiovascular disease. In: Braunwald's Heart Disease, Chapter 81, 8th Edition, 2008, pp. 2033-47.

Citation

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Healthy Ashkenazi centenarians have higher serum TSH levels than healthy normal controls.

Atzmon G, Barzilai N, Hollowell JG, Surks MI, Gabriely I. Extreme longevity is associated with increased serum thyrotropin. J Clin Endocrinol Metab 2009;94:1251-4.

SUMMARY

BACKGROUND Recent studies indicate that serum thyrotropin (TSH) concentrations increase with age. It remains uncertain whether this is due to a decline in thyroid function or an alteration in the TSH set point in elderly persons or another as yet unidentified factor. As a consequence, some professional societies have recommended that elderly patients with elevated serum TSH levels be treated. The aim of this study was to determine whether the shift in serum TSH concentrations with aging extends to centenarians and to assess the relationship between the concentrations of TSH and free thyroxine (FT_4) levels in this group.

METHODS The study population was recruited from the previously described Longevity Genes Study at Albert Einstein College of Medicine, Bronx, NY. A group of 232 independently living Ashkenazi Jewish centenarians were recruited to participate in this study. The study group comprised 166 women with a median age of 97.8 years and 66 men with a median age of 97.6 years. Their medical history, demographic characteristics, and clinical data were obtained using a structured questionnaire. All subjects underwent a physical examination and provided a blood sample. Individuals with acute or debilitating medical conditions or a history of thyroid disease or subjects taking thyroid medications or with serum TSH levels less than 0.4 μIU/ml with or without FT_4 levels outside the reference limits were excluded from the study. A group of 188 younger, unrelated Ashkenazi Jews were recruited to serve as the Ashkenazi control group, of which 95 were women (median age, 69.7 years) and 93 were men (median age, 72.3 years).

To exclude the possibility of an ethnicity-related bias in the interpretation of the data, another control group was obtained from the National Health and Nutrition Examination Survey (NHANES III) 1998 to 2002 data, which comprised all 605 subjects in the 60- to 79-year-old group who had serum TSH determinations and neither had thyroid disease nor were taking thyroid medications. All TSH and FT_4 analyses in the study subjects and the Ashkenazi controls were performed at the laboratories of Montefiore Medical Center, thus avoiding laboratory bias. However, because of

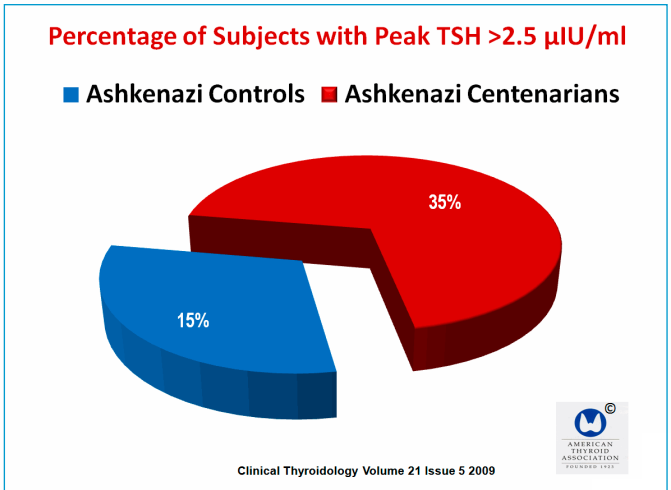

Figure 1. The percentage of subjects with peak serum TSH levels >2.5 μIU/ml was higher in the Ashkenazi centenarians as compared with Ashkenazi controls.

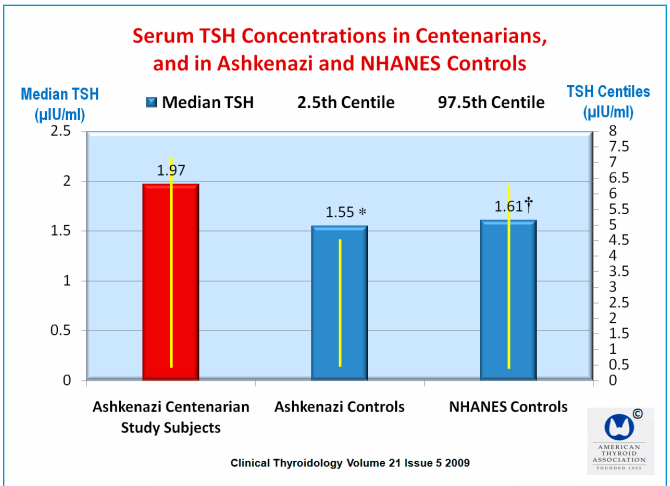

Figure 2. The serum TSH was significantly higher in the Ashkenazi centenarians as compared with the Ashkenazi and NHANES controls (*P<0.001 comparing centenarian study subjects with Ashkenazi controls and NHANES controls). The serum TSH concentrations were not statistically different in the Ashkenazi and NHANES controls (†P = 0.017 comparing the two control groups).

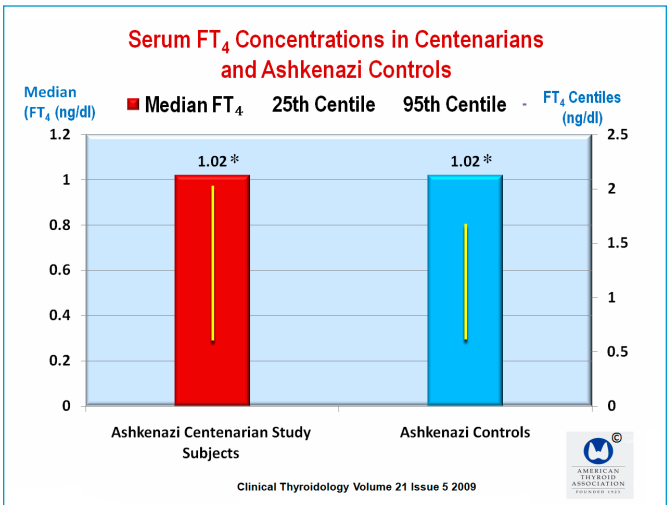

Figure 3. The median serum T_4 concentrations were similar in the centenarians and the Ashkenazi controls. *P = 0.37 comparing the two groups. There was an inverse correlation between TSH and FT_4 in the centenarians and the Ashkenazi control group (r = –0.27; †P = 0.02). FT_4 determinations were not available in the NHANES control group.

logistic and technical issues, serum TSH was analyzed in 232 centenarians and 185 controls, and serum FT_4 was analyzed in 137 centenarians and 172 controls, but only 97 centenarians and 150 controls had both serum TSH and FT_4 analyzed. In addition, antithyroid antibody levels were not determined in the study population because of insufficient availability of serum.

RESULTS The TSH was greater than 2.5 μIU/ml in 15.4% of the controls and 35.2% of the centenarians (Figure 1). Serum TSH was significantly higher in the Ashkenazi centenarians (median, 2.5 and 97.5 centiles) [1.97 (0.42 to 7.15 μIU/ml] as compared with the Ashkenazi controls [1.55 (0.46 to 4.55) μIU/ml] and the NHANES controls [1.61 (0.39 to 6.29] μIU/ml]; (P<0.001), as well as the TSH levels in the individuals older than 80 years in NHANES III (1.9 μIU/ml).

The median serum TSH concentrations were similar in the Ashkenazi [1.55 [0.46 to 4.55 μIU/ml] and NHANES [1.61 [0.39 to 6.29] μIU/ml]) control groups (P = 0.018) (Figure 2). The TSH distribution did not differ significantly between the Ashkenazi and NHANES control groups (P = 0.17), but the TSH distribution in the centenarians was significantly shifted to higher serum concentrations as compared with Ashkenazi and NHANES control groups (P = 0.01 and P = 0.002, respectively). Although the frequency distribution curves for TSH appeared similar in shape, the curves shifted to higher TSH concentrations in the centenarians, including the peak TSH level.

The median serum FT_4 concentrations were similar in the centenarians (1.02 [0.62 to 2.02] ng/ml) and Ashkenazi control group (1.02 [0.63 to 1.67] ng/ml) (P = 0.37) (Figure 3). There was an inverse correlation between TSH and FT_4 in the centenarians (r = –0.27; P = 0.02) and the Ashkenazi control group (r = –0.17; P = 0.47). However, FT_4 determinations were not available in the NHANES group. A stepwise regression model demonstrated that none of the medications that centenarians were taking had any significant effect on TSH levels.

CONCLUSION Ashkenazi centenarians have significantly higher median serum TSH levels than younger Ashkenazi controls.

COMMENTARY

The findings in this study are both very important and very intriguing. The data in this study demonstrate that centenarians have significantly higher median serum TSH concentrations than younger Ashkenazi controls. Moreover, the TSH distribution in the centenarians was shifted toward higher TSH levels, further emphasizing the fact that the majority of the centenarian population had higher serum TSH values as compared with the Ashkenazi control group. Furthermore, the NHANES data in all 605 subjects in the 60- to 79-year-old group were used to form an additional control group to avoid an ethnicity-related effect on serum TSH concentrations that might be overlooked if only the Ashkenazi control group were used in the study. In fact, the median serum TSH concentrations and distributions were comparable in the Ashkenazi and NHANES controls, verifying that the results were not biased by the ethnicity of the centenarians and Ashkenazi controls. Furthermore the serum TSH determinations for the centenarian and Ashkenazi control populations were performed at the same laboratory, excluding laboratory-related bias.

An earlier analysis of the TSH distribution in the U.S. population (NHANES III) (1) found a progressive increase in the median serum TSH concentrations with aging. A more recent study by Surks and Hollowell (2) demonstrated that the serum TSH distribution progressively shifts toward higher concentrations with age and that the prevalence of subclinical hypothyroidism may be significantly overestimated unless an age-specific range for TSH is used. In another study, Boucai and Surks (3) found that the reference limits for TSH differ between races and with age, and that the use of race- and age-specific reference limits decreases misclassification of patients with decreased or raised TSH in an urban practice. In the current study, the median TSH concentrations in the centenarian study group (1.97 μIU/ml) was higher than that in Ashkenazi or NHANES controls, including controls older than 80 years in NHANES III, demonstrating that the progressive population increase in serum TSH with aging includes centenarians. The findings by Surks and Hollowell support the findings in other studies that demonstrate an elevated serum TSH concentration in people with extreme longevity. For example, a study by Ravaglia et al. (4) of 44 healthy Northern Italian subjects ranging in age from 90 to 107 years, found that the study subjects had higher serum TSH levels (P<0.01) with lower free triiodothyronine/FT_4 ratios as compared with younger subjects. However, Surks and Hollowell state that the data in their study should be interpreted with caution because the reported studies have smaller numbers of subjects, some living in areas of variable iodine deficiency, and have different genetic backgrounds; thus the study by Surks and Hollowell should not be extrapolated to populations outside the United States.

Why there is a progressive increase in serum TSH concentrations with aging, including centenarians, remains uncertain. The authors suggest that this could be the result of several phenomena, including age-related alterations in TSH glycosylation, atrophic nonautoimmune thyroid changes, or an altered negative feedback set point. Moreover, they acknowledge that it is possible that the same FT_4 and TSH concentrations in aging individuals might have been present at a younger age.

Whether patients with subclinical hypothyroidism should be treated remains a subject of great controversy. Surks and Hollowell underscore two recent meta-analyses that provide conflicting views concerning the influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease. One study (5), designed to investigate whether age and sex influence the prevalence, incidence, and mortality of ischemic heart disease in people with subclinical hypothyroidism found that the incidence and prevalence of ischemic heart disease were higher in individuals with subclinical hypothyroidism as compared with euthyroid participants, but this held only for those younger than 65 years of age and not for subjects age 65 years or more.

Another meta-analysis (6) of subclinical thyroid dysfunction and the risk for coronary heart disease and mortality found that the relative risk (RR) for subclinical hypothyroidism for coronary heart

disease was 1.20 (95% confidence interval (CI), 0.97 to 1.49), and risk estimates were lower when higher-quality studies were pooled (RR, 1.02 to 1.08) and were higher among participants younger than 65 years (RR, 1.51 [95% CI, 1.09 to 2.09] for studies with a mean participant age less than 65 years and 1.05 [95% CI, 0.90 to 1.22] for studies with a mean participant age of 65 years or older). In an accompanying editorial, Ladenson (7) opined that, on the basis of these studies, the independent risk for coronary heart disease posed by subclinical hypothyroidism seems to be very modest, if it exists at all, and that only an appropriately powered prospective, randomized, controlled, double-blind interventional trial of thyroxine therapy for subclinical hypothyroidism can answer this question with the certainty that patients and their physicians deserve—which is feasible and should be done.

In accord with the comments by Ladenson, Surks and Hollowell concluded that until these issues are settled by future research, it seems prudent not to routinely treat elderly patients with levothyroxine because they are found to have a minimal increase in serum TSH. This is sound advice coming from strong evidence.

Ernest L. Mazzaferri, MD, MACP

References

1. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489-99.

2. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 2007;92:4575-82.

3. Boucai L, Surks MI. Reference limits of serum TSH and free T_4 are significantly influenced by race and age in an urban outpatient medical practice. Clin Endocrinol (Oxf) 2008;70:788-93.

4. Ravaglia G, Forti P, Maioli F, et al. Blood micronutrient and thyroid hormone concentrations in the oldest-old. J Clin Endocrinol Metab 2000;85:2260-5.

5. Razvi S, Shakoor A, Vanderpump M, et al. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. J Clin Endocrinol Metab 2008;93:2998-3007.

6. Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med 2008;148:832-45.

7. Ladenson PW. Cardiovascular consequences of subclinical thyroid dysfunction: more smoke but no fire. Ann Intern Med 2008;148:880-1.

The low serum T_3 level of the euthyroid sick syndrome is related to changes in stress cardiomyopathy

Lee SJ, Kang JG, Ryu OH, Kim CS, Ihm SH, Choi MG, Yoo HJ, Hong KS. The relationship of thyroid hormone status with myocardial function in stress cardiomyopathy. Eur J Endocrinol/ EJE-08-0808 [Pii] 10.1530/EJEJ 2009[doi]

SUMMARY

BACKGROUND Thyroid hormone exerts many actions on cardiac function and peripheral vascular tone. Myocardial contractility is decreased by overt hypothyroidism, and in turn, impaired myocardial contractility reduces thyroid hormone metabolism. In addition, subclinical hypothyroidism also impairs left ventricular diastolic function, which returns to normal with thyroid hormone–replacement therapy. There also is information that the low T_3 serum levels in patients with the euthyroid sick syndrome (ESS) may have an influence on cardiac function. The aim of this study was to investigate thyroid hormone status and its relationship with myocardial function and the biochemical parameters in stress cardiomyopathy.

METHODS The study group comprised 45 patients with stress cardiomyopathy treated at the Hallym University Sacred Heart Hospital in Korea from January 2003 through December 2006. The two control groups were as follows: control group I consisted of 58 healthy subjects with no previous history of thyroid or cardiac disease, and group II consisted of 31 patients who had the same underlying diseases as the patient group without stress cardiomyopathy. The patient group had been hospitalized for at least 3 months prior to the study, and none were treated with drugs affecting thyroid function, such as amiodarone, dopamine, and glucocorticoids, at the time of admission and during hospitalization. The causes of stress cardiomyopathy were community-acquired pneumonia (in 24 patients), uncompensated hepatic disease (in 13), urinary tract infections (in 6), and sepsis of unidentified origin (in 2). At the time of hospital admission, all the patients had coronary angiography showing no significant coronary artery stenosis or spasm. ESS was defined as normal serum thyrotropin (TSH) levels with serum triiodothyronine (T_3) levels below the lower normal range (80 to 200 ng/dl). Myocardial dysfunction was defined as a left ventricular ejection fraction (LVEF) less than 50%. Within 24 hours of admission, the Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated. Echocardiographic examination and thyroid hormone measurements were performed at the time of hospital admission and were repeated after full recovery 6 months later. All patients were treated according to the underlying disease and were fully recovered without sequelae at the time of the study.

RESULTS The patient group comprised 45 patients, 14 men and 31 women with a mean (±SD) age of 63±12 years. The first APACHE II score was 11±1.8 and the mean hospital stay was 23±14 days. The LVEF and systolic but not diastolic blood pressure were significantly decreased at the time of admission, as compared with the tests in the control group I and the patient group after full recovery ($P<0.05$ for both observations). At the time of admission, troponin I, creatine kinase–myoglobin (CK-MB), and β-natriuretic peptide (BNP) were significantly increased as compared the tests in control groups I and II ($P<0.05$ for both groups) (Figure 1).

At the time of hospital admission, 62.2% of the patient group had ESS, with significantly decreased serum total T_3 levels but

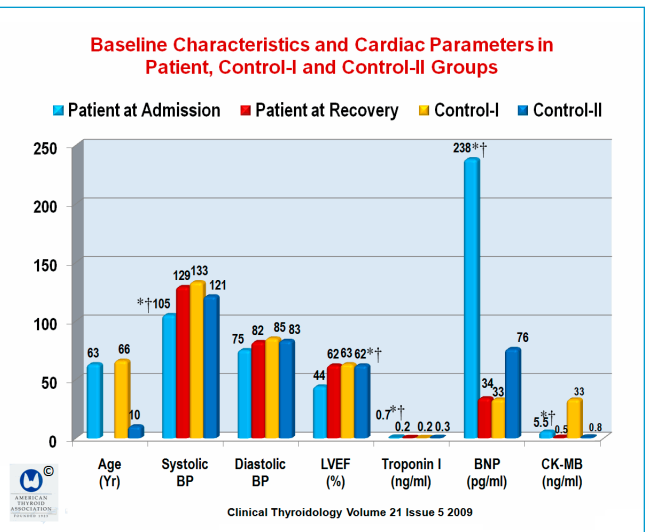

Figure 1. Troponin, serum CK-MB and BNP were significantly increased (*P<0.05) at the time of admission vs. control group I and vs. control group II; †P<0.05). Systolic blood pressure (BP) levels were significantly suppressed in patients at the time of admission vs. patients at full recovery and subjected in both control groups (derived from data in Table 1 of Lee et al.).

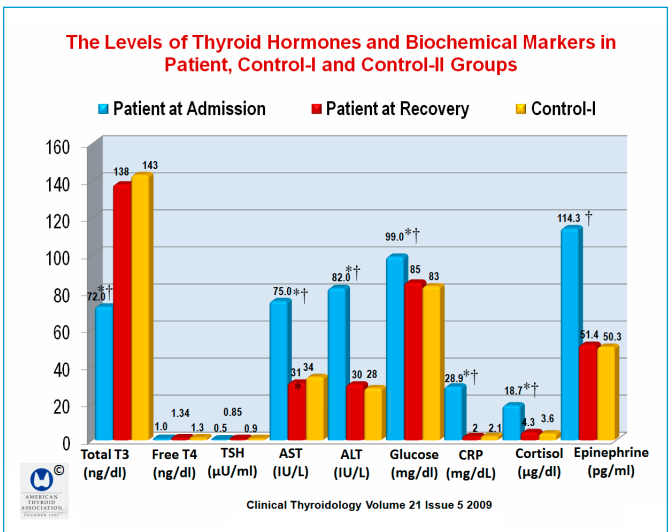

Figure 2. In addition to the levels shown, those of norepinephrine and dopamine were also significantly elevated at the time of admission as compared with the patient group at full recovery and control groups I and II. *P<0.05. †P<0.05. (Derived from data in Table 2 of Lee et al.)

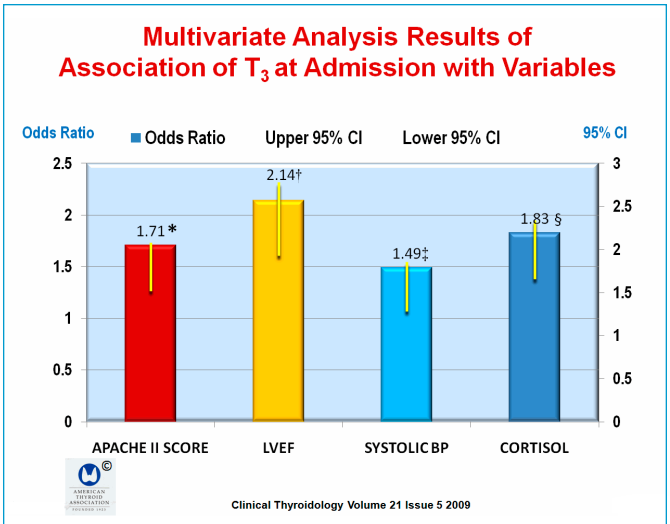

Figure 3. Multivariate analysis findings are expressed as odds ratios for an association of serum T_3 at the time of hospital admission as compared with APACHE scores. LVEF = left ventricular ejection fraction; BP = systolic blood pressure at the time of admission. *P = 0.037. †P = 0.015. ‡P = 0.041. §P = 0.026. All P values are for significance of odds ratio.

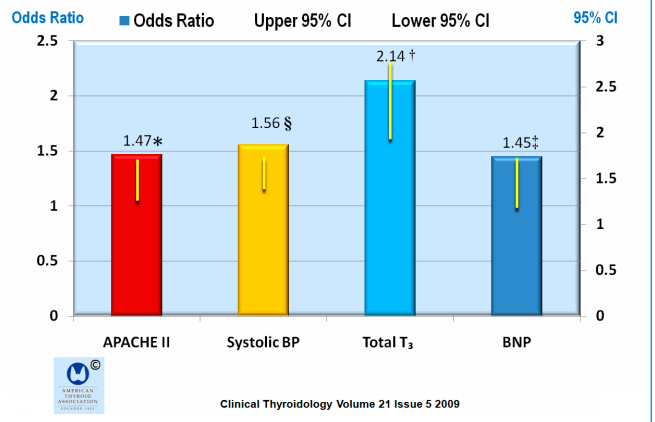

Figure 4. Multivariate analysis findings for an association of LVEF at the time of admission as compared with other patient and laboratory variables at the time of admission. *P = 0.032. †P = 0.028. ‡P = 0.015. §P = 0.04. BNP = β-natriuretic peptide.

normal T_4 and TSH levels (P<0.05), as compared with those in control group I and the patient group at the time of full recovery. In addition, antithyroid peroxidase antibody (TPOAb) positivity but not titer was significantly elevated as compared with control group I (P<0.05). Also at the time of admission, the serum levels of alanine amino transferase (ALT) aspartate transaminase (AST), glucose, C-reactive protein (CRP), and cortisol, were all significantly higher as compared with those in control group I and the patient group at the time of full recovery (P<0.05 for all); in addition, plasma levels of epinephrine, norepinephrine, and dopamine were all significantly higher at admission as compared with the levels in patients at the time of full recovery (Figure 2).

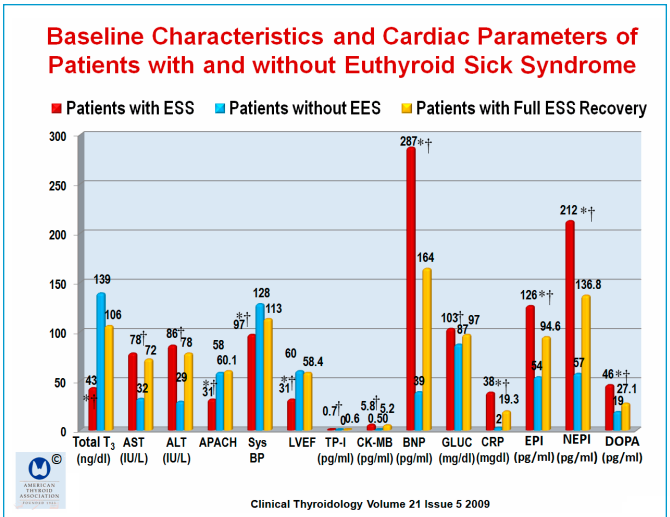

Figure 5. Baseline characteristics for patients with ESS showing serum aspartate transaminase (AST), alanine transaminase (ALT), APACHE II (APACH) systolic blood pressure (Sys BP) LVET left ventricular ejection time, troponin I (TPI), β-natriuretic peptide (BNP), C-reactive protein (CRP) epinephrine (EPI), norepinephrine (NEPI), and dopamine (DOPA) See Figure 1 legend for P values. (Derived from Tables 3 and 4 of Lee et al.)

Multivariate analysis found that total T_3 levels at the time of admission were significantly associated with the APACHE II score (odds ratio [OR], 1.71; 95% confidence limits [CI], 1.52 to 2.08); P = 0.037), LVEF (OR, 2.14; 95% CI, 1.93 to 2.78; P = 0.015), systolic blood pressure (OR, 1.49; 95% CI, 1.28 to 1.86; P = 0.041), and cortisol (OR, 1.83; 95% CI, 1.66 to 2.34; P = 0.026) (Figure 3). In control group II, the total T_3 levels were not associated with any variables by multivariate analysis, nor did the free thyroxine and TSH levels have any relation to the clinical or biochemical parameters in the patients or in control groups II and II. (Figure 4)

After the patient group was classified into two subgroups, the ESS group (n = 28) and non-ESS group (n = 17) , the time of hospitalization was found to be longer in the ESS group (25±12 vs. 20±8 days), and the APACHE II score, systolic BP, LVEF, troponin, CK-MB, and BNP were all significantly different in the ESS and non-ESS groups (P<0.05) (Figure 5).

When the patient group was subclassified into one with (n = 27) and one without (n = 18) myocardial dysfunction, the following were found to be significantly different in the two groups: APACHE II score, systolic blood pressure, troponin I, CK-MB, and BNP (P<0.05). In each subgroup, systolic blood pressure, troponin I, CK-MB, and BNP levels at the time of admission were also significantly different at the time of admission as compared with the same variables in the full-recovery group (P<0.05 for all). At the time of admission, serum total T_3 levels were significantly decreased in the myocardial dysfunction group as compared with the subjects without myocardial dysfunction (P<0.05). After full recovery, there was no difference in cardiac and biochemical markers between the patients and control group I, the ESS subgroups, and the myocardial dysfunction groups.

CONCLUSION The low serum T_3 level of ESS is related to changes in stress cardiomyopathy.

COMMENTARY

Endocrinologists are likely not to be familiar with stress cardiomyopathy, largely because it seems to be so far from our day-to-day activities. However, this article by Lee et al. brings this syndrome to our attention. In the early 1990s, Japanese physicians began reporting a unique, reversible cardiomyopathy that seemed to be precipitated by acute emotional stress (1). The stress cardiomyopathies as a group appear similar in that they seem to occur during times of enhanced sympathetic tone and may be precipitated by catecholamine stimulation of the myocardium. This syndrome was initial given the name Takotsubo cardiomyopathy (TC), but more recently has been referred to as apical ballooning syndrome or broken heart syndrome. The syndrome now has been reported worldwide and has been acknowledged by the American Heart Association as a unique form of reversible cardiomyopathy (2). In a systematic review, women 62 to 75 years of age accounted for 82% to 100% of patients with TC, but the syndrome has been described in individuals from 10 to 91 years of age (3). The presentation of TC is usually similar to an acute coronary syndrome with ischemia-like chest pain and abnormal ECG changes mimicking ischemia. Precipitants of stress cardiomyopathy include acute emotional stress, acute intracranial events, and acute medical illness, including sepsis, surgical procedures, and overproduction of catecholamines (pheochromocytoma). Apical and midventricular left ventricular dysfunction is common but this may extend to global left ventricular hypokinesis. The formal diagnostic criteria have not yet been fully accepted, but include transient left ventricular motion abnormalities, absence of obstructive coronary artery disease, and new electrocardiographic abnormalities.

It has long been recognized that thyroid disease exerts serious effects on the heart and cardiovascular system (4), and the role of serum T_3 is becoming more prominent in this disorder. Iervasi and the cardiothoracic research group from Pisa have shown that low serum T_3 levels are the most significant predictor of cardiovascular and all-cause mortality in patients with heart disease. A recently published randomized, placebo-controlled study by the group (5) has shown that short-term levothyroxine-replacement therapy significantly improves the neuroendocrine profile and ventricular performance of patients with chronic heart failure.

The main findings in the study by Lee et al. are that low serum T_3 levels with normal free T_4 and TSH levels were associated with a decrease in the LVEF, which supports the notion that low total T_3 levels are correlated with myocardial contractility and dysfunction in patients with stress cardiomyopathy and reinforces the idea that ESS may play a major role in stress cardiomyopathy.

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References

1. Tsuchihashi K, Ueshima K, Uchida T, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. J Am Coll Cardiol 2001;38: 11-8.

2. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. Circulation 2008;118:397-409.

3. Bybee KA, Kara T, Prasad A et al. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. Ann Intern Med 2004;141:858-65.

4. Klein I. Thyroid hormone and cardiac contractility. Am J Cardiol 2003;91:1331-2.

5. Pingitore A, Galli E, Barison A, et al. Acute effects of triiodothyronine (T_3) replacement therapy in patients with chronic heart failure and low-T_3 syndrome: a randomized, placebo-controlled study. J Clin Endocrinol Metab 2008;93:1351-8.

Patients with papillary microcarcinoma that extends into soft tissues or is metastatic to locoregional lymph nodes are at high risk for persistent or recurrent disease

Mercante G, Frasoldati A, Pedroni C, Formisano D, Renna L, Piana S, Gardini G, Valcavi R, Barbieri V. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. Thyroid 19:1-10.1089/thy.4-6-2009.0270 [doi]

SUMMARY

BACKGROUND The initial management of papillary thyroid microcarcinoma (PTMC) is controversial, mainly because the 10-year cancer-specific mortality rates with this tumor are vanishingly small, in the range of 1% to 2%. This study is aimed at defining the clinical course of this disease and the prognostic factors for tumor recurrence and distant metastases.

METHODS The study subjects were patients with PTMC selected from a group of 1030 patients surgically treated for papillary thyroid carcinoma in the Department of Otolaryngology in the Thyroid Disease Center in Reggio Emilia, Italy, from 1978 through 2003. PTMC was defined as a tumor ≤1 cm as described by the World Health Organization classification and documented in the final surgical histology. All patients were initially treated with total thyroidectomy or lobectomy plus isthmusectomy (partial thyroidectomy) and had completion thyroidectomy if at least one of the following was present: age ≥45 years, tumor multifocality, extrathyroidal extension, lymph-node metastases, or aggressive histologic variants of papillary thyroid cancer such as columnar cell, tall cell, or solid tumor. Partial thyroidectomy was performed only in patients younger than 45 years and without tumor multifocality, extrathyroidal extension, and lymph-node metastases or without aggressive histologic variants. Beginning in 1993, all patients had neck ultrasonography for presurgical assessment of cervical lymph-node metastases. Prior to 1996, level VI cervical lymph-node compartment dissections were performed only when lymph-node metastases were identified preoperatively or during surgery; however, after 1996 all patients with presurgical cytologic evidence of PTMC had total thyroidectomy with pretracheal and ipsilateral paratracheal lymph-node dissection if a frozen-section specimen revealed metastases in a dissected lymph node. Patients with lymph-node metastases in the lateral compartments underwent a modified neck dissection in cervical lymph-node-compartment levels II and IV. Thyroid capsular invasion was defined as tumor extension into the surrounding soft tissues or the sternothyroid muscle. Thyroid extracapsular invasion was defined as a tumor infiltrating the thyroid capsule with invasion of the perithyroidal soft tissues or muscle. All patients had radioactive iodine (^{131}I) remnant ablation with 30 to 50 mCi (1110 to 1850 MBq). Nine to 12 months later, serum thyroglobulin (Tg) levels were measured and a diagnostic whole-body ^{131}I scan was performed after thyrotropin (TSH) withdrawal or recombinant human TSH injection to confirm successful ablation of thyroid remnants. During the first 5 years after initial treatment, follow-up was performed every 6 to 2 months, and every 12 to 24 months thereafter. Beginning in 1994, cervical ultrasonography was performed during follow-up. Patients were classified as being free of tumor if they had undetectable TSH-stimulated serum Tg levels without evidence of lymph-node metastases by ultrasonography and whole-body ^{131}I scintigraphy.

RESULTS The study population comprised 445 patients; 347 women (78%) and 98 men (22%). In 222 (49.9%) of the patients PTMC was diagnosed preoperatively by fine-needle aspiration biopsy, and in the other 223 cases (50.1%) the tumor

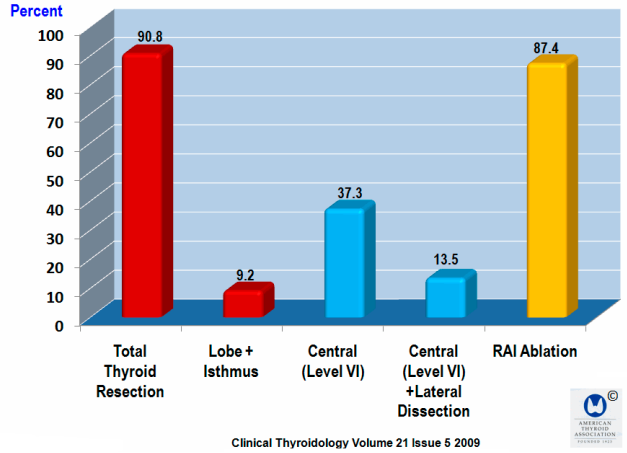

Figure 1. This is a summary of the initial therapy for 445 patients with papillary microcarcinoma. RAI = radioactive iodine.

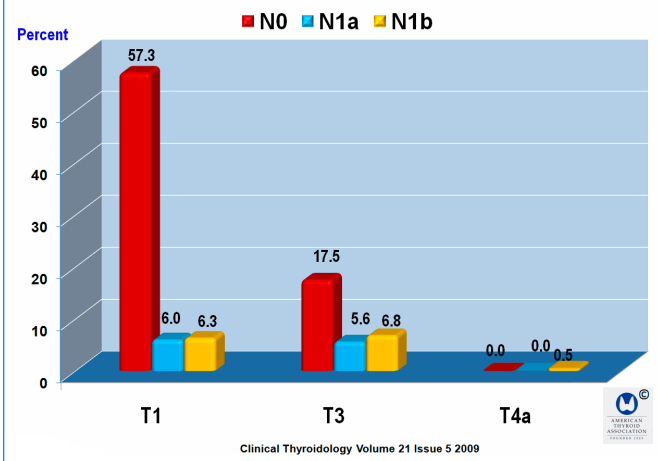

Figure 2. This is a summary of the tumor stage in 445 patients. pT1 = tumor 2 cm or less in greatest dimension limited to the thyroid gland; N0 = no lymph-node metastases ; N1a = ipsilateral lymph-node metastases; N1b = metastases in bilateral, midline or contralateral or mediastinal lymph nodes; T_3 = tumor > 4 cm or any tumor with minimal extrathyroid extension; T_4a = tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.

Figures 3 and 4. These figures show the characteristics of the study patients and tumor characteristics of the papillary microcarcinomas in this study.

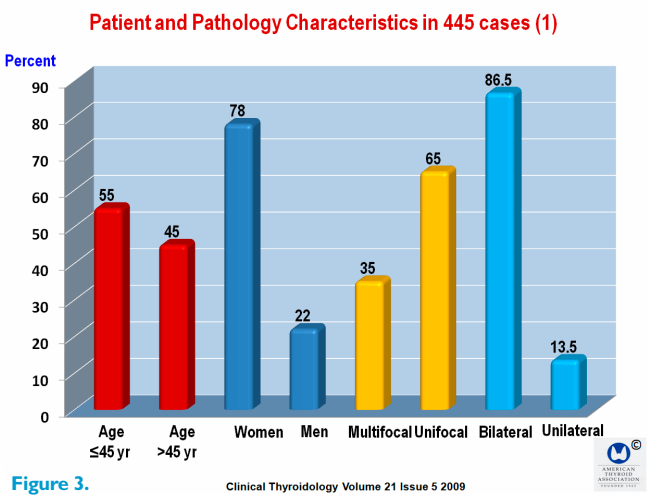

Figure 3.

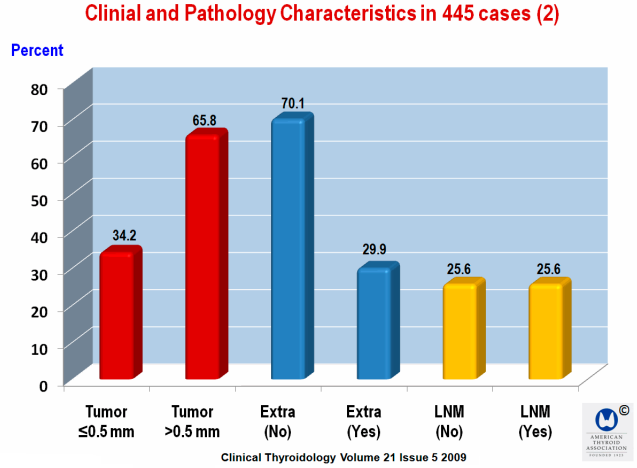

Figure 4. (LNM is lymph-node metastasis.)

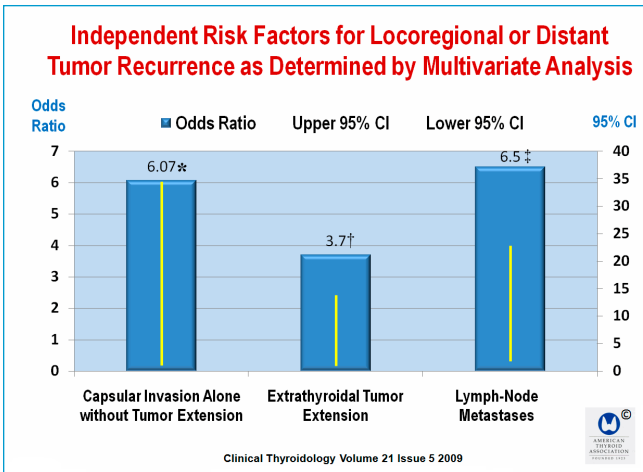

Figure 5. This figure shows a summary of the independent risk factors for locoregional recurrence or persistent tumor, with or without distant metastases. *P = 0.04, †P = 0.049, and ‡P = 0.003 for odds ratios. CI = confidence interval.

was discovered in patients undergoing surgery for multinodular goiter (n = 103), follicular neoplasm (n = 99) or Graves' disease (n = 14). A total of 41 patients had partial thyroidectomy alone; total thyroidectomy was thus performed in 404 patients (90.8%) (Figure 1). Neck lymph-node compartment dissection was performed in 226 patients (49.7%), of whom 166 (73%) did not have presurgical evidence of lymph-node metastases but underwent a level VI (central) compartment dissection with total thyroidectomy, while 60 patients(27%) with presurgical evidence of cervical lymph-node metastases had central compartment and lateral neck dissection with total thyroidectomy (Figure 1). The tumor node, metastasis (TNM) stage distribution is shown in Figure 2. The patient characteristics and the clinical and pathologic characteristics of tumor are shown in Figures 3 and 4. The surgical histology showed that 312 patients (70.1%) had classic papillary thyroid cancer, 117 (26.3%) had follicular variant papillary thyroid cancer, 4 (0.9%) had follicular cancer, and 1 (0.9%) had papillary cancer with medullary thyroid cancer. After a mean follow-up of 5.3 years (range, 1 to 26), 17 patients (3.8%) had recurrence or persistent disease: neck recurrence was found in 12 patients (2.7%), distant metastases occurred in 4 patients (0.9%), and 1 patient had neck recurrence and distant metastases. Only 6 (46%) of the neck recurrences were identified by neck ultrasonography. One patient (0.2%) died of the disease.

Univariate analysis in the 389 patients eligible for statistical analysis found that the presence of extrathyroidal tumor extension (pT_3) with or without lymph-node metastases (N0 or N1) at the time of diagnosis was related to locoregional cervical and distant tumor recurrences ($P<0.05$). The rate of tumor recurrence or persistent disease was observed more often in pT_3 as compared with pT1 tumor stage ($P = 0.02$). The rate of tumor recurrence (11.6%) in patients with lymph-node metastases (N1) was significantly higher than the rate in patients without lymph-node metastases (pN0; $P = 0.02$). The rates of cervical and distant recurrences were more frequent in patients with thyroid tumor capsular invasion without extrathyroidal extension (8.1% vs. 3.6%), which was not statistically significant ($P = 0.06$).The rate of neck recurrence (0.9%) was the same in patients who underwent elective level VI dissection as compared with patients who did not undergo this procedure.

Multivariate analysis identified three independent prognostic risk factors related to the persistence or recurrence of locoregional PTMC tumor with or without distant metastasis, which were as follows: (a) a sixfold risk for recurrence with capsular invasion without extrathyroidal tumor extension (odds ratio [OR], 6.07; 95% confidence interval [CI], 1.06 to 34.5; $P = 0.04$); (b) a 3.7-fold risk for recurrence with extrathyroidal tumor extension at the time of diagnosis (OR, 3.7; 95% CI, 1 to 13.9; $P = 0.049$); and (c) a 6.5-fold risk for recurrence in patients with lymph-node metastases at the time of diagnosis (OR, 6.5; 95% CI, 1.8 to 22.9; $P = 0.003$) (Figure 5). Age, sex, tumor bilaterality, and tumor diameter >5 mm or ≤5 mm were not significant factors for recurrence.

CONCLUSION Patients with papillary microcarcinoma that extends into the thyroid capsule, with or without extrathyroidal tumor extension or with lymph-node metastases, are at higher than usual risk for tumor recurrence or persistence of disease that should be treated with total thyroidectomy and radioiodine therapy.

COMMENTARY

Papillary microcarcinomas comprise almost half of the thyroid cancers that have been diagnosed in the United States during the past three decades (1). The sheer numbers of these small tumors has sparked substantial debate, concerning initial management of papillary microcarcinoma, with opinions ranging from no therapy (watchful waiting) (2) or lobectomy alone for incidentally discovered papillary microcarcinomas, unless the tumor is multifocal, has aggressive histology (e.g., tall-cell carcinoma), is metastatic, or is found in patients with a history of head and neck irradiation or familial tumor (3), in which case total thyroidectomy is advised. Patients with papillary microcarcinoma are rarely treated with radioiodine (^{131}I), although tumor that is aggressive, invasive, and metastatic would prompt some to suggest ^{131}I therapy (4,5). The nuances concerning the features and management of these small tumors have sparked much of the debate.

One of the issues that seems to be disregarded regularly is the nuances concerning the definition of papillary microcarcinoma and the risk for poor outcome. The World Health Organization's definition of papillary microcarcinoma is a papillary tumor, which is found incidentally, that measures 1 cm or less in diameter. Many authors ignore the fact that papillary microcarcinoma, by definition, is a tumor that is found incidentally (6). The second problem relates to staging risk for papillary microcarcinomas. The sixth edition of TNM staging system, which is endorsed by the American Joint Commission on Cancer and the International Union Against Cancer have changed the definition of T1 from a tumor of 1 cm or less in diameter to a tumor of 2 cm or less, which renders the pathological definition of papillary microcarcinoma no longer consistent with the WHO pathological definition, according to the WHO classification of tumors (6). Moreover, the TNM definition of stage I papillary thyroid cancer in a patient younger than 45 years is a tumor of any size, with or without lymph-node metastases, in effect rendering locoregional lymph-node metastases of no prognostic importance. Most patients would not agree with this definition.

Why are these issues important? A seminal study by Bilimoria et al (7) of slightly over 52,000 patients with papillary cancer, among whom 12,469 had tumors <1 cm, found that 10-year recurrence rates for these subcentimeter tumors were 4.6% and the 10-year cancer-specific mortality rate was 2%. However, there was little information about tumor invasion or lymph-node metastases in the group with subcentimeter tumors. The main outcome concerning this group of tumors was that total thyroidectomy did not confer an advantage measured in terms of recurrence and cancer-specific mortality.

A study by Noguchi et al. (8) of 2070 patients with papillary microcarcinoma in which the median follow-up was 15.1 years and was as long as 35 years in some patients provides important information on tumor recurrence. The main findings were that the 30-year recurrence rates were 40% in patients older than 55 years. Multivariate analysis found that four variables independently predicted recurrence: (a) absence of autoimmune thyroid disease, (b) gross lymph-node metastases, (c) tumor size >5 to 10 mm, and (d) esophageal tumor invasion. The 35-year recurrence rates were 3% for tumors 1 to 5 mm, and 14% for tumors 6 to 10 mm ($P<0.001$). The recurrence rates were 20% and 5%, for patients with and without gross lymph-node metastases ($P<0.001$); and the recurrence rates were 40% and 6%, for patients with and without esophageal tumor invasion ($P<0.001$). The number of grossly enlarged lymph nodes was inversely related to recurrence-free survival. The 30-year recurrence rates were less than 10% in patients younger than 55 years and 40% for patients 55 years or older. The main conclusion of this study was that papillary microcarcinomas larger than 5 mm that are invasive and metastatic have a high recurrence rate, especially among older patients without thyroid autoimmune disease.

A recent meta-analysis of papillary microcarcinoma by Roti et al. (9) found that tumor recurrence was significantly associated with age <45 years ($P<0.04$) and with clinically overt papillary microcarcinomas ($P<0.001$), but was not related to tumor size) but tumor multifocality and lymph-node metastases at the time of diagnosis were highly significant factors related to recurrence ($P<0.001$).

There is relatively little information about the efficacy of lymph-node dissection in patients with papillary microcarcinoma. Mercante et al. performed neck lymph-node compartment dissection in 226 patients (50%), of whom 166 (73%) did not have presurgical evidence of lymph-node metastases but had a total thyroidectomy with prophylactic level VI (central) cervical compartment dissection, while 60 (27%) others with presurgical evidence of cervical lymph-node metastases had total thyroidectomy with therapeutic central compartment and lateral neck dissections. It is difficult to identify the effect of initial therapy—thyroid surgery, lymph-node compartment dissections, and radioiodine therapy—in a group of patients with papillary microcarcinoma, half of whom had their tumor discovered during surgery for multinodular goiter (n = 103).

The American Thyroid Association guideline recommendations for initial therapy for patients with papillary microcarcinoma are as follows:

- R26: For patients with thyroid cancer larger than 1 cm, the initial surgical procedure should be a near-total or total thyroidectomy unless there are contraindications to this surgery. Thyroid lobectomy alone may be sufficient treatment for small (<1 cm), low- risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or radiologically or clinically involved cervical nodal metastases. Recommendation A

- R27a1 Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central or lateral neck lymph nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. Recommendation B

- R27b1 Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T_3 or T_4). Recommendation C

- R27c1 Near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T_2), noninvasive clinically node-negative papillary thyroid cancers, and most follicular cancer. Recommendation C

These recommendations provide guidance for the spectrum of initial findings in patients with papillary microcarcinoma.

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References

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.

2. Ito Y, Miyauchi A. A therapeutic strategy for incidentally detected papillary microcarcinoma of the thyroid. Nat Clin Pract Endocrinol Metab 2007;3:240-8.

3. Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109-42.

4. Mazzaferri EL. Management of low risk differentiated thyroid cancer. Endocr Pract 2007;13:498-512.

5. Chow SM, Law SC, Chan JK, et al. Papillary microcarcinoma of the thyroid—prognostic significance of lymph node metastasis and multifocality. Cancer 2003;98:31-40.

6. DeLellis RA, Lloyd RV, Heitz PU, Eng C. World Health Organization classification of tumours: pathology and genetics; tumors of endocrine organs. Lyons, France: IARC Press International Agency for Research on Cancer, 2004.

7. Bilimoria KY, Bentrem DJ, Ko CY. et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg 2007;246:375-84.

8. Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. World J Surg 2008;32:747-53.

9. Roti E, degli Uberti EC, Bondanelli M, et al. Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. Eur J Endocrinol 2008;159:659-73.

In addition to increased diagnostic activity, other environmental factors may contribute to the rising incidence of papillary thyroid cancer

Rego-Iraeta A, Perez-Mendez LF, Mantinan B, Garcia-Mayor RV. Time trends for thyroid cancer in northwestern Spain: true rise in the incidence of micro and larger forms of papillary thyroid carcinoma. Thyroid 2009;19:333-40.

SUMMARY

BACKGROUND The incidence of thyroid cancer has been rising over the past three decades in the United States and in many other areas around the world. Although a variety of factors may be responsible for this trend, some have attributed it mainly to the increased utilization of sensitive diagnostic techniques such as neck ultrasonography and fine-needle aspiration biopsy. However, there is growing awareness that there may be other as yet unidentified factors that might be responsible for this increased incidence of thyroid cancer. The aims of this retrospective study were to define the incidence and prevalence of thyroid cancer in Vigo, Spain, from 1979 through 2001 and to investigate the relationship between the incidence and prevalence rates of thyroid cancer and the trends in tumor size and thyroid surgery over time.

METHODS Data were obtained from the Pathology Registry of the Vergo University Hospital, which belongs to the Spanish public health system that collects data on about 97% of the malignant tumors verified by microscopic examination. The study population comprises 322 cases of papillary, follicular, Hürthle-cell, and medullary thyroid cancer. Tumor stages were classified according to the 1992 tumor–node–metastasis (TNM) staging classification. Papillary thyroid cancers ≤1 cm were categorized as papillary thyroid microcarcinoma (PTMC).

RESULTS During the study period, 2345 patients had thyroidectomies, which represented a significant increase from 13.76 (95% confidence interval [CI], 12.35 to 14.56) to 23.83 (95% CI, 22.17 to 24.73) to 45.01 (95% CI, 42.45 to 46.39) cases per 100,000 persons each year from 1978 to 1985, 1986 to 1993, and 1994 to 2001, respectively. The proportion of thyroid cancers among patients who had a thyroidectomy increased from 9.92% in 1978 to 1985, to 12.31% in 1986 to 1993, and to 15.35% in 1994 to 2001, respectively (P = 0.015). Total thyroidectomy comprised 48% of the initial surgical procedures in 1978 to 1985, and 74% during 1994 to 2001. A total of 322 thyroid cancer cases were diagnosed from 1978 to 2001. Mean patient age at the time of diagnosis was 46.8 years (range, 8 to 91). The ratio of women to men was 3.6 to 1. Of the 322 cases, 245 (76%) were papillary, 44 (13.7%) follicular, 23 (7.1%) medullary, and 10 (3.1%) anaplastic thyroid cancers. The papillary-to-follicular cancer ratio was 5.8; when PTMC cases were excluded, this ratio was 2. PTMC cases increased significantly over time, rising to 16.7%, 23%, and 43% during 1978 to 1985, 1986 to 1993, and 1994 to 2001, respectively (Figure 1). The ratio of papillary thyroid cancer to follicular thyroid cancer increased significantly over time from 2.3 to 3.6 to 11.5, respectively; when PTMC was excluded, these ratios increased over time from 1.9 to 2.7 to 6.6, respectively.

Trends in thyroid cancer incidence in men and women and by age: The rates of thyroid cancer were considerably higher in women than in men. The overall incidence of thyroid cancer increased significantly in women from 1.61 to 4.43 to 10.29 cases per 100,000 from 1978 to 1985, 1986 to 1993, and 1994 to 2001, respectively (Figure 2). The age-standardized incidence rates (ASRs) over this period show the same tendency, with a

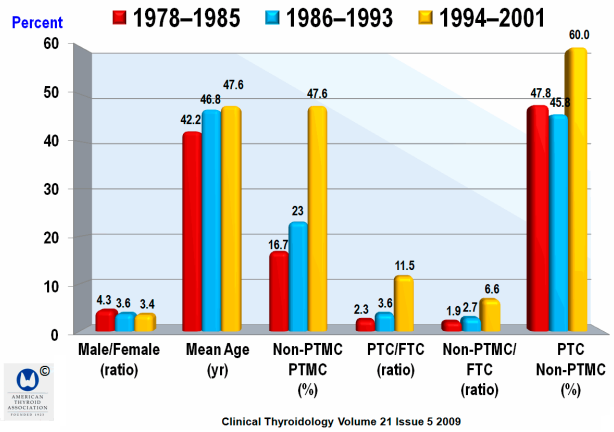

Figure 1. This figure summarizes the male-to-female ratio in thyroid cancer over time, the mean age of patients during this period, and the proportion of papillary and follicular thyroid cancers. FTC = follicular thyroid cancer; PTMC = papillary thyroid microcarcinoma; PTC = papillary thyroid carcinoma without PTMCs. The data in this figure are derived from Table 1 of Rego-Iraeta et al.

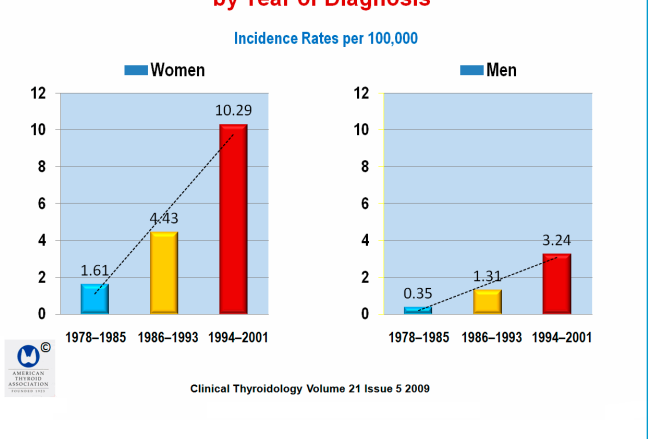

Figure 2. The unadjusted thyroid cancer incidence rate from 1978 through 2001 has been rising in Spain, particularly in women. The incidence rates were approximately threefold higher in women than in men. The line represents the rising incidence over time. The data in this figure are derived from Table 2 of Rego-Iraeta et al.

Age-Adjusted Thyroid Cancer Incidence Rates in Women and Men by Year of Diagnosis

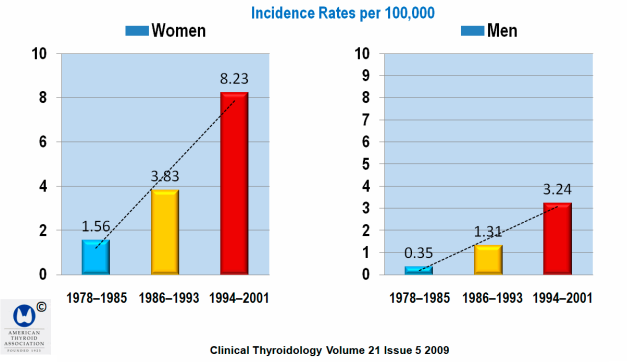

Figure 3. The age-adjusted increase in the incidence rates of thyroid cancer in women from 1978 through 2001 are approximately 2.5-fold those of men. The data in this figure are derived from Table 4 of Rego-Iraeta et al.

Papillary Thyroid Cancer Incidence Rates of Tumors Larger than 1 cm and Papillary Microcarcinomas in Women

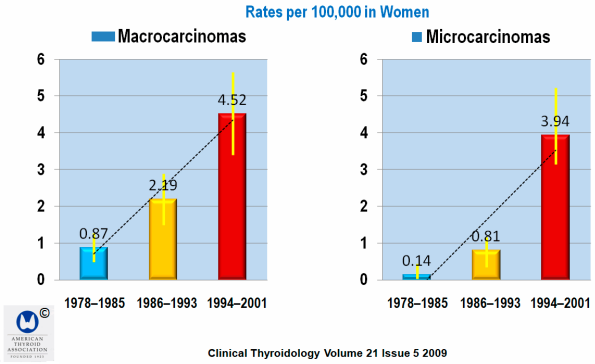

Figure 5. The incidence rates of tumors 1 cm or smaller (papillary thyroid microcarcinoma) and that of larger papillary thyroid carcinomas are almost the same. The bars = 95% CI, and the line = trend in the increase of macro- and microcarcinomas. The Data in men are comparable. The data in this figure are derived from Table 3 of Rego-Iraeta et al.

Time Trend of Thyroid Cancer Prevalence by Sex

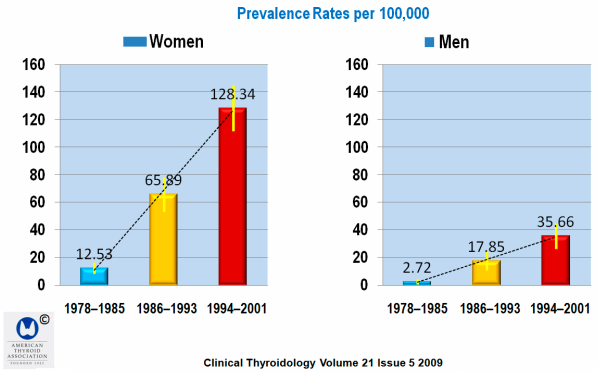

Figure 4. The age-adjusted prevalence rates of thyroid cancer in women are approximately threefold those of men. The yellow bars show the 95% confidence limits, and the line shows the approximately tenfold increase in the prevalence of thyroid cancer among woman and men during 1978 through 2001. The data in this figure are derived from Table 4 of Rego-Iraeta et al.

significant increase in women in the incidence of thyroid cancer of 1.56 per 100,000 each year (1978 to 1985) to 3.83 (1986 to 1993) and 8.23 (1994 to 2001); for men the incidences were 0.33, 1.19, and 2.65 (Figure 3). The prevalence rates of thyroid cancer have shown a comparable increase from 1978 to 2001. Figure 4 shows that the prevalence of thyroid cancer increased substantially between 1985 and 2001 in both sexes.

Trends in thyroid cancer incidence by histopathology: The increase in papillary thyroid cancer is the result of an increased incidence of both PTMC and papillary thyroid cancer, which occurs in both men and women (Figure 5).

CONCLUSION The increasing incidence of thyroid cancer in Spain is equal to the rise in papillary microcarcinoma, and there has not been a shift over time in the thyroid cancer tumor size except for that of papillary microcarcinoma. In addition to increased diagnostic activity, these trends may reflect the contribution of other environmental factors

COMMENTARY

The incidence of thyroid cancer in the United States and in many regions around the world has been steadily increasing over the past three decades. The American Cancer Society estimates that 37,340 new cases occurred in 2008, about 75% of which were in women, and the rates were twice as high among white patients as black patients. Why this increase in thyroid cancer has occurred has engendered considerable debate. Davies and Welch (1) investigated the size distribution of papillary thyroid cancers in approximately 24,000 thyroid cancer cases in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) thyroid cancer registry from the years 1988 to 2002, 88% of which were papillary thyroid cancers. They found that the incidence of thyroid cancer increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002, a 2.4-fold increase ($P<0.001$ for trend) that was virtually completely due to papillary cancer, which increased from 2.7 to 7.7 per 100,000, a nearly threefold increase ($P<0.01$ for trend). There was no significant change in the incidence of follicular, medullary, and anaplastic thyroid cancer ($P>0.2$ for trend). The authors found that between 1988 and 2002, the bulk of the increasing incidence was from the detection of small papillary thyroid cancers. In all, nearly half of the tumors (49%) were ≤1 cm and 87% were ≤2 cm. Still, the papillary thyroid cancer mortality rates from 1973 through 2002 were stable, at approximately 0.5 death per 100,000. The authors concluded that this is predominantly due to the increased detection of small papillary cancers, which, combined with the flat mortality rates, suggests that this is an artifact produced by a reservoir of subclinical disease, not a true occurrence of thyroid cancer.

Several others have reached similar conclusions. Kent et al. (2), in a study from Canada, also found that carcinoma increased over the 12-year period. A significantly higher number of small (≤2 cm), nonpalpable tumors were resected in 2001 than in 1990 (P = 0.001), while the incidence of tumors 2 to 4 cm in diameter remained stable. When they examined the differences in tumor-detection rates by age and sex, they found a disproportionate increase in the number of small tumors among women and patients older than age 45 years. As a result, the authors suggested that more frequent use of medical imaging has led to an increased detection rate of small, subclinical tumors, which in turn accounts for the higher incidence of differentiated thyroid carcinoma

The study by Rego-Iraeta et al. has, according to the authors, three main points: (1) the increased incidence of thyroid cancer occurred equally in papillary microcarcinoma and in tumors larger than 1 cm; and (2) except for papillary microcarcinoma, there has not been a shift over the past two decades in thyroid tumor size in patients living in Spain; and (3) there has not been a similar increase in thyroid tumors of other histologic types. The authors suggest that these trends may reflect the contribution of other environmental factors in addition to enhanced diagnostic activity. The authors reach a conclusion similar to that of Enewold et al., (3) which also found that the SEER incidence rates of the smallest tumors (≤1 cm) increased 248% and increased 222% in those with the largest tumors (>5 cm). They found that 50% of the overall increase in papillary cancer incidence rates collected from the SEER program were due to tumors ≤2.0 cm, and 30% could be attributed to cancers 1.1 to 2.0 cm, and 20% to cancers >2 cm. When they made the assumption that all the increases in thyroid cancer were caused by the very small tumors, they could estimate that about 50% could be attributed to enhanced diagnostic accuracy; however, if there were changes in other potential risk factors, then the estimate for the role of early detection causing the increased incidence of thyroid cancer would be considerably lower. Among white women, the rate of increase for cancers >5 cm almost equaled that for the smallest papillary cancers. They concluded that medical surveillance and more sensitive diagnostic procedures cannot completely explain the observed increases in papillary thyroid cancer rates and that other possible explanations should be explored.

This and the study by Enewold provide strong support for the notion that the increase in thyroid cancer that has occurred over the past three decades may be due to one or more environmental factors that have yet to be identified.

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References

1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006;295:2164-7.

2. Kent WD, Hall SF, Isotalo PA, et al. Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. CMAJ 2007;177:1357-61.

3. Enewold L, Zhu K, Ron E, et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980-2005. Cancer Epidemiol Biomarkers Prev 2009;18:784-91.

Patients with papillary thyroid cancer have significantly reduced serum parathyroid hormone levels after prophylactic central neck compartment dissection

Roh JL, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. Ann Surg 2007;245:604-10.

SUMMARY

BACKGROUND Although lymph-node metastases are common in papillary thyroid cancer, there is considerable debate concerning the use of routine prophylactic central neck dissection (CND) for all patients undergoing total thyroidectomy. The debate mainly stems from the fact that there are no robust data regarding either the benefit or the complications of prophylactic lymph-node dissection. The aim of this retrospective study was to investigate the pattern of lymph-node metastases, morbidity, and recurrence rates after bilateral CND with or without lateral neck dissection (LND).

METHODS The study subjects were 155 patients who had total thyroidectomy from 2001 through 2004 for papillary thyroid cancer at the Asian Medical Center of the University of Ulsan College of Medicine in Seoul, Korea. Patients who had prior neck surgery, unilateral lobectomy, and subtotal or completion thyroidectomy were excluded from the study. Data were collected on patient demographics, surgical procedures, the number of parathyroid glands preserved or autotransplanted, and the presence of symptoms of hypocalcemia. Devascularized parathyroid glands confirmed by frozen-section analysis were transplanted into the sternocleidomastoid muscle. Postoperatively, patients were routinely monitored for symptoms of hypocalcemia and abnormal serum calcium and parathyroid hormone (PTH) levels. CND (without microdissection methods) was performed cranially to both superior thyroid arteries and the pyramidal lobe and caudally to the innominate vein, laterally to the carotid sheaths, and dorsally to the prevertebral fascia. The central compartment was divided into four node sites: pretracheal, ipsilateral, contralateral paratracheal, and to the superior mediastinal area below the sternal notch. Parathyroid autotransplantation was performed as required, not routinely. Preoperative baseline blood samples were obtained on the morning of surgery for measurements of serum ionized calcium, total calcium, and intact PTH levels. Postoperative serum calcium was measured 1, 8, 24, 48, and 72 hours after surgery. Hypocalcemia was defined as a symptomatic ionized serum calcium level <1.0 mmol/L during hospitalization or at any time after discharge. Patients in whom hypocalcemia developed were treated with oral calcium, vitamin D, and if necessary, intravenous calcium gluconate.

RESULTS Of the 155 study patients, 130 (84%) were women and 25 (16%) were men; the mean age was 47 years (range, 18 to 75). Patients were divided into two groups, one with 82 patients (53%) who had total thyroidectomy and bilateral CND, and the other with 73 patients (47%) who had total thyroidectomy without CND. Sex, age, and MACIS (metastases, age, completeness of surgery, invasiveness, and size of the tumor) tumor scores were similar between the two treatment groups. The mean tumor size, the rate of tumor multifocality and extracapsular tumor invasion, and the number of patients with primary tumors ≤1 cm (papillary microcarcinoma), did not differ among the two treatment groups (Figure 1). Lymph-node metastases were found in the central neck in 51 (62%) of the CND group, and in 21 (25.6%) of the non-CND group (Figure 1). The rate of lymph-node metastases was higher in patients with tumor that extended beyond the thyroid capsule (29 of 45; 64%) than in patients with no tumor invasion (10 of

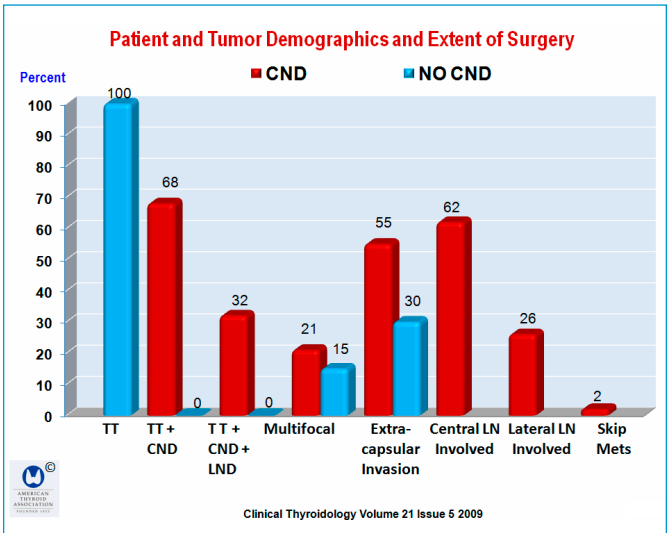

Figure 1. The tumor demographics are shown in patients who did or did not have central neck dissection (CND). TT = total thyroidectomy; LND = lateral lymph-node dissection; LN = lymph nodes; Mets = metastases. Here and elsewhere the percentages are rounded to an integer.

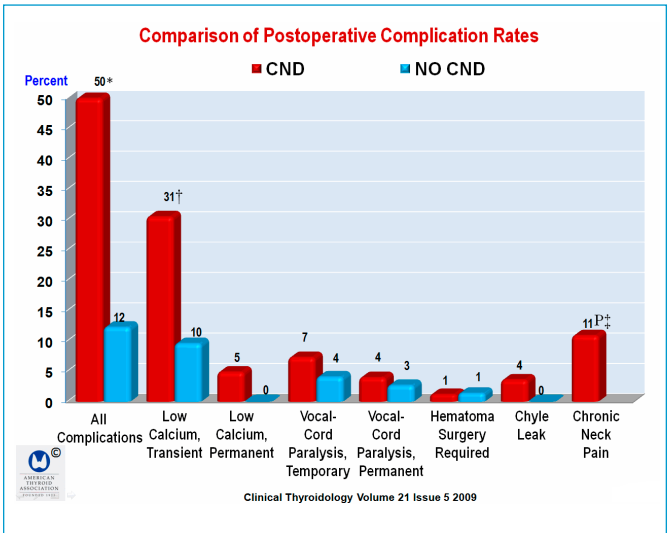

Figure 2. This figure shows the complication rates among patients who did or did not have central neck dissection (CND). *P<0.001, †P = 0.001, ‡P = 0.004, comparing patients who did with those who did not have central neck dissection.

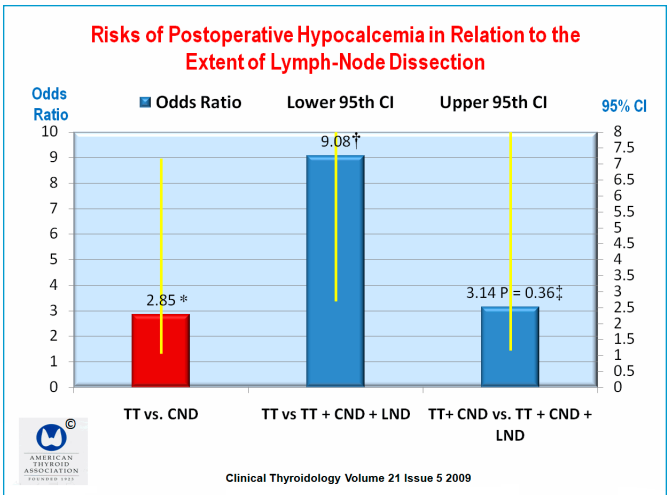

Figure 3. This figure shows the risk (odds ratios) for postoperative hypocalcemia with various forms of surgery. TT = total thyroidectomy alone; CND = central neck dissection; LND = lateral neck dissection; yellow lines = 95% confidence intervals. *P<0.001, †P = 0.001, ‡P = 0.01, comparing patients who did with those who did not have central neck dissection.

37; 27%, P = 0.001). Among 70 patients with a primary tumor located in a thyroid lobe, 47 (67%) had central compartment metastases that involved the ipsilateral paratracheal (62%), pretracheal (33%), superior mediastinal (20%), and contralateral (13%) sites. Of 12 patients with tumors originating in the thyroid isthmus, 4 (33%) had central lymph node compartment metastases that involved the pretracheal (25%), paratracheal (17%), and mediastinal (8%) sites.

Parathyroid glands were found in the thyroid or central lymph-node specimens from 16 patients (10%) who had CND; the mean number of parathyroid glands that were incidentally removed was 1.2, the frequency of which did not differ between the two treatment groups (P = 0.180). The complication rate was higher in the CND group than the no-CND group (50% vs. 12.3%, respectively; P<0.001) (Figure 2). Four patients in the CND group required calcium supplements 1 year after surgery. Vocal cord paralysis occurred in 9 (6%) patients, 5 of whom had permanent vocal-cord paralysis due to intentional resection of a unilateral recurrent laryngeal nerve involved with tumor invasion. Other complications included postoperative bleeding that required surgery in 2 patients (1.3%), chyle leakage in 3 (3.6%), and longstanding pain in the operated lateral neck in 9 (34%), some of whom also had chronic shoulder pain (Figure 2). The risk for postoperative hypocalcemia in different surgical procedures is shown in Figure 3.

Although preoperative levels of serum calcium and PTH were similar, those who had neck lymph-node compartment dissections had a greater decline in mean serum calcium levels as compared with patients who did not have lymph-node dissections (12% vs. 7.6%; P = 0.002). Serum calcium levels were lower within 1 day after surgery for the lymph-node dissection group as compared with those who did not have lymph-node dissections. Still, for both groups, serum calcium levels were nearly normal within 3 months after surgery. The serum PTH levels decreased in most patients within an hour after surgery. The mean serum intact PTH levels declined more in the lymph-node-dissection group than in the no-lymph-node-dissection group (66% vs. 41%; P= 0.001), with PTH concentrations of 13.9 and 24.9 pg/ml in the two groups, respectively, which remained low for 7 days and slowly recovered within 6 months after surgery. The PTH concentration decreased to 24.9 pg/ml after surgery without lymph-node dissections and remained low for 7 days, recovering to preoperative levels within 1 month after surgery. For the group that had lymph-node dissections, PTH concentrations decreased

The mean (±SD) duration of follow-up was 51±25 and 53±28 months in patients who had CND and those who did not have CND, respectively (P = not significant). After a mean of 48 months, cancer recurrence developed in 4 patients (2.6%), 1 in the central neck alone and 3 in both the central and lateral neck compartments. Three patients who did not have lymph-node dissection had recurrences in the central compartment alone (n = 1) or the central and lateral compartments (n = 2), and all subsequently underwent CND or CND plus LND. Except for one patient with distant metastases, all patients became free of disease.

CONCLUSION Patients with papillary thyroid cancer who have prophylactic central neck compartment dissections have significantly reduced serum parathyroid hormone levels.

COMMENTARY

Although this is not a recent publication, it was highlighted in this issue of Clinical Thyroidology to emphasize the wide range of complications that may be associated with prophylactic lymph-node dissection. As the debate surrounding this topic increases, we must continue to consider the broad spectrum of experiences that have been reported with this surgical procedure.

This is a careful analysis of the morbidity, recurrence, and postoperative serum calcium and PTH levels in patients who had total thyroidectomy with prophylactic CND and, in some cases, LND. The study demonstrates the extent to which complications may occur with CND. Half the patients who had lymph-node dissections experienced complications, as compared with only 12% of patients who had total thyroidectomy alone. Transient hypocalcemia occurred in 32% of the CND group and only 10% of the total thyroidectomy group without CND; the hypocalcemia was permanent in 5% and 0%, respectively. Temporary vocal-cord paralysis occurred in 7% and 4% of the two groups, and permanent paralysis in 4% and 3%, respectively. The only difference between the two treatment groups that was statistically significant occurred with transient hypocalcemia (P = 0.001). Postoperative hypocalcemia and a rapid decline in serum PTH concentrations occurred more commonly in the prophylactic lymph-node-dissection group than in those who did not have lymph-node dissections. After performing this study, the authors concluded that prophylactic central and lateral compartment lymph-node dissections should not be recommended, because of the high rate of complications.

Henry et al. (1) compared the morbidity of total thyroidectomy with prophylactic central neck dissection in 50 patients with papillary thyroid carcinoma with that in 50 patients who were treated for multinodular goiter. None of the patients in the entire study

developed permanent laryngeal-nerve paralysis, although two patients (4%) in the lymph-node-dissection group and three (6%) in the total thyroidectomy group developed transient laryngeal-nerve paralysis. Transient hypoparathyroidism occurred in 7 (14%) of the central lymph-node-dissection group and 4 (8%) of the total thyroidectomy group, which became permanent in 2 patients (4%) in the central lymph-node-dissection group. The authors concluded that it is difficult to advocate routine central neck dissection, even when taking into account the possible benefits.

Another study of 342 patients with papillary thyroid carcinoma by Scheumann et al. (2) found that systematic lymph-node dissection of cervical lymph-node metastases improved recurrence ($P<0.001$) and survival ($P<0.005$), especially in patients with T1 to T_3 tumors (1 to >4 cm). The authors concluded that compartment-oriented dissection of lymph-node metastases results in enhanced survival and a lower tumor-recurrence rate.

White et al. (3) performed a systematic review of the literature concerning central lymph-node dissection in patients with differentiated thyroid cancer. Using evidence-based criteria, the authors reached several important conclusions.

- Systematic compartment-oriented central lymph-node dissection may decrease the recurrence of papillary thyroid cancer and likely improves disease-specific survival (grade C recommendation).
- Limited level III data suggest survival benefit with the addition of prophylactic dissection to thyroidectomy (grade C recommendation).
- The addition of total thyroidectomy can significantly reduce levels of serum thyroglobulin and increase the rates of undetectable serum thyroglobulin levels (level IV data, no recommendation).
- There may be a higher rate of permanent hypoparathyroidism and unintentional permanent nerve injury when central lymph-node dissection is performed with total thyroidectomy than for total thyroidectomy alone (grade C recommendation).
- Reoperation in the central neck compartment for recurrent papillary thyroid carcinoma may increase the risk of hypoparathyroidism and unintentional nerve injury as compared with total thyroidectomy with or without central lymph-node dissection (grade C recommendation), supporting a more aggressive initial operation.

The authors concluded that evidence-based recommendations support central lymph-node dissection for patients with papillary thyroid carcinoma under the care of experienced endocrine surgeons.

A recent and very important study by Bonnet et al. (4) comprised 115 patients with papillary thyroid carcinoma less than 2 cm without ultrasonographically detectable cervical lymph nodes were treated with total thyroidectomy and complete selective dissection of the central and lateral neck compartments. This was aimed at determining the effect of surgical lymph node staging on the indication for radioiodine treatment. The main finding was that precise lymph-node staging by prophylactic neck dissection of tumors initially staged T1N0 favorably modified the indication for radioiodine ablation for 30% of patients. In this study, vocal-cord paralysis and hypoparathyroidism each occurred in only 0.9% of cases.

In summary, the initial therapy for patients with papillary thyroid cancer has been gradually changing, with increasingly more emphasis on prophylactic lymph-node dissection. Whether patients will accept extensive prophylactic neck lymph-node compartment surgery for what appears to be low-risk tumor remains uncertain. Still, despite the low mortality rates with these tumors, the recurrence rates are high. It is thus unlikely that many patients will forgo both remnant ablation and prophylactic lymph-node compartment dissection if informed of the high rate of preoperatively unrecognized lymph-node metastases.

As with the learning curve that occurred with total thyroidectomy, extensive lymph-node compartment surgery must be provided by well trained and highly experienced surgeons. The Bonnet study shows a way to blend cervical lymph-node dissection with the accurate selection of patients for postoperative radioiodine therapy. Much of the predictable controversy over this issue is likely to sound similar to the decades-old arguments concerning lobectomy versus total thyroidectomy.

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References

1. Henry JF, Gramatica L, Denizot A, et al. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. Langenbecks Arch Surg 1998;383:167-9.

2. Scheumann GF, Gimm O, Wegener G, et al. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. World J Surg 1994;18:559-68.

3. White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer. World J Surg 2007;31:895-904.

4. Bonnet S, Hartl D, Leboulleux S, et al. Prophylactic Lymph Node Dissection for Papillary Thyroid Cancer Less than 2 cm: Implications for Radioiodine Treatment. J Clin Endocrinol Metab 2009;94:1162-7.

REVIEWS

1. Chisholm EJ, Kulinskaya E, Tolley NS.Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. Laryngoscope 2009.

2. Chao M, Jiawei X, Guoming W, Jianbin L, Wanxia L, Driedger A, Shuyao Z, Qin Z.Radioiodine treatment for pediatric hyperthyroid Grave's disease. Eur J Pediatr 2009.

3. Gyamfi C, Wapner RJ, D'Alton ME.Thyroid dysfunction in pregnancy: the basic science and clinical evidence surrounding the controversy in management. Obstet Gynecol 2009;113:702-7.

4. Mehanna HM, Jain A, Morton RP, Watkinson J, Shaha A.Investigating the thyroid nodule. BMJ 2009;338:b733.

5. Layfield LJ, Cibas ES, Gharib H, Mandel SJ.Thyroid aspiration cytology: current status. CA Cancer J Clin 2009;59:99-110.

6. Mendelson AA, Al-Khatib TA, Julien M, Payne RJ, Black MJ, Hier MP.Thyroid gland management in total laryngectomy: meta-analysis and surgical recommendations. Otolaryngol Head Neck Surg 2009;140:298-305.

7. Bizhanova A, Kopp P.Minireview: The sodium-iodide symporter NIS and pendrin in iodide homeostasis of the thyroid. Endocrinology 2009;150:1084-90.

8. Chiamolera MI, Wondisford FE.Minireview: Thyrotropin-releasing hormone and the thyroid hormone feedback mechanism. Endocrinology 2009;150:1091-6.

9. Kung B, Aftab S, Wood M, Rosen D.Malignant melanoma metastatic to the thyroid gland: a case report and review of the literature. Ear Nose Throat J 2009;88:E7.

10. Ma C, Kuang A, Xie J.Radioiodine therapy for differentiated thyroid carcinoma with thyroglobulin positive and radioactive iodine negative metastases. Cochrane Database Syst Rev 2009;CD006988.

HOT ARTICLES

11. Fast S, Nielsen VE, Grupe P, Bonnema SJ, Hegedus L.Optimizing ^{131}I Uptake After rhTSH Stimulation in Patients with Nontoxic Multinodular Goiter: Evidence from a Prospective, Randomized, Double-Blind Study. J Nucl Med 2009;50:732-7.

12. Fast S, Nielsen VE, Bonnema SJ, Hegedus L.Time to reconsider nonsurgical therapy of benign non-toxic multinodular goitre: focus on recombinant human TSH augmented radioiodine therapy. Eur J Endocrinol 2009;160:517-28.

13. Regalbuto C, Marturano I, Condorelli A, Latina A, Pezzino V.Radiometabolic treatment of hyperthyroidism with a calculated dose of 131-iodine: results of one-year follow-up. J Endocrinol Invest 2009;32:134-8.

14. Schneider AB, Viana MA, Ron E.Weighing shadows: can meta-analysis help define the risk-benefit ratio of RAI treatment for low-risk thyroid cancer patients? Thyroid 2009;19:435-6.

15. Ascheim DD, Hryniewicz K.Thyroid hormone metabolism in patients with congestive heart failure: the low triiodothyronine state. Thyroid 2002;12:511-5.

16. Bengel FM, Nekolla SG, Ibrahim T, Weniger C, Ziegler SI, Schwaiger M.Effect of thyroid hormones on cardiac function, geometry, and oxidative metabolism assessed noninvasively by positron emission tomography and magnetic resonance imaging. J Clin Endocrinol Metab 2000;85:1822-7.

17. Vos X, Smit N, Endert E, Tijssen J, Wiersinga W.Variation in phenotypic appearance of Graves' disease: effect of genetic anticipation and duration of complaints. Eur J Endocrinol 2009.

18. Bauer M, Silverman DH, Schlagenhauf F, London ED, Geist CL, Van HK, Rasgon N, Martinez D, Miller K, Van HA, Berman SM, Phelps ME, Whybrow PC.Brain Glucose Metabolism in Hypothyroidism: A Positron Emission Tomography Study Before and After Thyroid Hormone Replacement Therapy. J Clin Endocrinol Metab 2009.

DISCLOSURE

Dr. Mazzaferri receives honoraria from Genzyme for providing lectures.

Dr. Sipos receives honoraria from Abbott and Genzyme for providing lectures.