

## TOP 20 - THYROID ARTICLES

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The following is a list of twenty outstanding articles which have occurred in the thyroid literature during the past few years. These articles have been selected by Jerome M. Hershman, M.D., prior editor of "Thyroid" Journal.

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### Screening for Thyroid Dysfunction

- 1 -- **Canaris GJ, Manowitz NR, Mayor G, Ridgway EC.**  
**The Colorado thyroid disease prevalence study.**  
**Arch Intern Med. 2000; 160:526-34.**

25,862 participants in a statewide health fair in Colorado in 1995 were evaluated for thyroid dysfunction. The prevalence of elevated TSH levels in this population was 9.5%, and the prevalence of decreased TSH levels was 2.2%. Six percent were taking thyroid hormone. Of those not on therapy, hypothyroidism was found on 0.4%, subclinical hypothyroidism in 8.5%, hyperthyroidism in 0.1%, and subclinical hyperthyroidism in 0.9%. The survey discloses the high frequency of thyroid functional disease in our population,

- 2 -- **Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, Smith SA, Daniels GH:**  
**American Thyroid Association guidelines for detection of thyroid dysfunction.**  
**Arch Intern Med. 2000; 160:1573-5.**

The Standards of Care Committee of the American Thyroid Association recommends that all adults over age 35 be screened for thyroid dysfunction by TSH measurement every 5 years.

- 3 -- **Ross DS (ed)**  
**Assessment of thyroid function and disease.**  
**Endocrinol Metab Clin North Am. 2001 June; 30:245-528**

This volume contains excellent reviews of all of the thyroid diagnostic tests.

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# Hypothyroidism

- 4 -- **Haddow JE, Palomaki GE, Allan WC, et al.**  
**Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child.**  
**N Engl J Med 1999 Aug 19; 341(8):549-55**

The neuropsychological performance of children, age 8, whose mothers had elevated TSH during pregnancy, were compared with progeny of mothers with normal TSH. The children of mothers with untreated hypothyroidism had lower IQ and scored lower than the control children in 7 of 13 tests of intellectual ability and school performance. I believe the results indicate that pregnant women should have TSH measurement and be treated if TSH is elevated.

In a subsequent paper they reported that of those with TSH>6 mU/L, the incidence of fetal death was 4.4-fold greater than in those with normal TSH.  
(Allan WC, Haddow JE, Palomaki GE, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 2000; 7(3):127-30)

- 5 -- **Singh N, Singh PN, Hershman JM.**  
**Effect of calcium carbonate on the absorption of levothyroxine.**  
**JAMA 2000 Jun 7; 283(21):2822-5**

Nalini Singh and her colleagues at the VA Greater Los Angeles Healthcare System showed that, when calcium carbonate was ingested with levothyroxine, it reduced the absorption of the levothyroxine, resulting in elevation of serum TSH. Since many post-menopausal women with hypothyroidism also take calcium carbonate for osteoporosis, it is important to advise that the levothyroxine and calcium carbonate are not ingested simultaneously.

- 6 -- **Arafah BM.**  
**Increased need for thyroxine in women with hypothyroidism during estrogen therapy.**  
**N Engl J Med 2001 Jun 7; 344(23):1743-9**

In a group of 18 postmenopausal women on thyroxine replacement therapy, treatment with estrogen increased serum TSH and decreased the free T4 levels. In 7 of the 18, serum TSH increased to more than 7 mU/L. The author concludes that estrogen therapy increases the need for levothyroxine replacement in some women with hypothyroidism.

- 7 -- **Cooper DS.**  
**Clinical practice. Subclinical hypothyroidism.**  
**N Engl J Med 2001 Jul 26; 345(4):260-5**

David Cooper has written an excellent review of subclinical hypothyroidism. The bottom line: nearly all patients with elevated serum TSH should be given a trial of thyroid hormone therapy.

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# Thyroid Cancer

- 8 -- **Haugen BR, Pacini F, Reiners C, et al.**  
**A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant of cancer.**  
**J Clin Endocrinol Metab 1999 Nov; 84(11):3877-85**

This is the result of the second phase 3 trial of recombinant human TSH for evaluation of patients with differentiated thyroid cancer. Scans after recombinant hTSH were almost as frequently positive as those after withdrawal of thyroid hormone; the difference between the two methods was not significant. Combining stimulated thyroglobulin with scanning detected all recurrences..

- 9 -- **Hundahl SA, Cady B, Cunningham MP, et al.**  
**Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996.**  
**Cancer 2000 Jul 1; 89(1):202-17.**

The American College of Surgery cancer database collected 5,583 cases of thyroid carcinoma treated in the US during 1996. The data show that the relative frequencies of the different cancers are: 81% papillary, 10% follicular, 3.6% Hurthle cell, 0.5% familial medullary, 2.7% sporadic medullary, and 1.7% anaplastic. Surprisingly, only 53% of the cases had fine-needle aspiration of the thyroid gland. (FNA should be performed in nearly all patients with thyroid nodules before surgery.) The vast majority of patients with differentiated thyroid carcinoma presented with Stage I and II disease and relatively small tumors. For all histologies, near-total or total thyroidectomy constituted the dominant surgical treatment. Residual tumor after the surgery could be documented in 11% of cases, hypocalcemia in 10% of cases, and recurrent laryngeal nerve injury in 1.3% of cases. Complications were mostly frequently associated with total thyroidectomy combined with lymph node dissection. Thirty-day mortality was 0.3%; when anaplastic cancer cases were eliminated, it decreased to 0.2%.

- 10 -- **Bartolazzi A, Gasbarri A, Papotti M, et al.**  
**Application of an immunodiagnostic method for improving preoperative diagnosis of nodular thyroid lesions.**  
**Lancet 2001 May 26; 357(9269):1644-50.**

This study from the Karolinska Institute, the founding institution of thyroid FNA, tested immunostaining for galectin-3 on 1009 thyroid lesions (tissue specimens and cytological cell-blocks) and 226 fresh cytological samples obtained preoperatively by ultrasound-guided fine-needle aspiration of thyroid nodules (prospective analysis). The sensitivity and specificity of galectin-3 immunodetection in discriminating benign from malignant thyroid lesions were more than 99% and 98% respectively. Immunostaining for galactin 3 discriminated follicular carcinoma (positive stain). Papillary carcinomas were also positive. If this holds up in routine cytology labs, it will be a great advance in diagnosis.

- 11 -- Morris LF, Waxman AD, Braunstein GD.**  
**The nonimpact of thyroid stunning: remnant ablation rates in <sup>131</sup>I-scanned and nonscanned individuals.**  
**J Clin Endocrinol Metab 2001 Aug; 86(8):3507-11.**

Thyroid stunning has been reported as the temporary impairment of thyroid tissue after a 111-MBq (3 mCi) or greater diagnostic <sup>131</sup>I dose that decreases the final absorbed dose in ablative therapy. To assess whether a stunning effect has any impact on therapeutic outcomes, the authors compared initial treatment ablation rates in patients who received 111- to 185-MBq <sup>131</sup>I diagnostic scans (n = 37) before ablative doses of 3700-7400 MBq with ablation rates in patients who did not receive any <sup>131</sup>I before the initial treatment dose (n = 63). Ablation rates were 64.9% for scanned patients and 66.7% for nonscanned patients, a nonsignificant difference. Nonscanned patients with metastatic lesions (n = 23) were ablated at a higher rate (78.3%) than scanned patients (n = 9) (66.7%), but the difference was not significant (P = 0.50). It is possible that the reported stunning phenomenon, specifically its impact in temporarily impairing tissue, has been overemphasized. (However, quantitative studies show reduction of the uptake in therapy doses after previous diagnostic doses. This is still an unsettled issue.)

- 12 -- Pacini F, Agate L, Elisei R, Capezzone M, et al.**  
**Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic (<sup>131</sup>I) whole body scan: comparison of patients treated with high (<sup>131</sup>I) activities versus untreated patients.**  
**J Clin Endocrinol Metab 2001 Sep; 86(9):4092-7.**

Detectable serum Tg levels associated with negative diagnostic (<sup>131</sup>I) whole body scan are not infrequently found in patients with differentiated thyroid cancer. Several researchers have shown that in these patients the administration of high (<sup>131</sup>I) activity (100 mCi or more) increases the sensitivity of a posttherapy diagnostic (<sup>131</sup>I) whole body scan performed a few days later and allows the detection of neoplastic foci not seen with diagnostic doses of (<sup>131</sup>I). Empirical radioiodine treatment has also been advocated by some researchers, but its therapeutic effect is controversial. In our institute, positive serum Tg/negative diagnostic (<sup>131</sup>I) whole body scan patients were not treated with high (<sup>131</sup>I) activities before 1984; afterward, almost all patients with positive serum Tg/negative diagnostic (<sup>131</sup>I) whole body scan patients were treated with radioiodine, and a posttherapy diagnostic (<sup>131</sup>I) whole body scan was performed. In the present retrospective study the authors compared the outcome of these two groups of patients, 42 treated and 28 untreated, followed for mean periods of 6.7 +/- 3.8 and 11.9 +/- 4.4 yr, respectively. In the treated group the first posttherapy diagnostic (<sup>131</sup>I) whole body scan was negative in 12 patients and positive in 30 patients. (<sup>131</sup>I) treatment was further administered only in the latter group. At the end of follow-up in treated patients a complete remission (normalization of serum Tg off L-thyroxine and negative diagnostic (<sup>131</sup>I) whole body scan) was observed in 10 patients (33.3%). In 9 cases (30%) posttherapy diagnostic (<sup>131</sup>I) whole body scan became negative, and serum Tg was reduced but still detectable; in 11 patients (36.6%) serum Tg was detectable, and posttherapy diagnostic (<sup>131</sup>I) whole body scan was positive. The resolution of (<sup>131</sup>I) uptake in lung metastases was observed in 8 of 9 cases (88.8%) and in cervical node metastases in 11 of 18 cases (61.1%). In patients treated only once because the posttherapy diagnostic (<sup>131</sup>I) whole body scan was negative (n=12), 2 patients (16.7%) were in apparent remission, 7 (58.3%) had detectable Tg values without evidence of disease, 2 (16.7%) showed lymph node metastases in the mediastinum, and 1 patient (8.3%) died because of lung metastases. Of the 28 untreated patients, none with radiological evidence of disease, serum Tg off L-thyroxine therapy became undetectable in 19 cases (67.9%), significantly reduced in 6 cases (21.4%), and unchanged or increased in 3 patients (10.7%), 1 of whom developed lung metastases 14 yr after the diagnosis.

In summary, the results indicate that in patients with detectable serum Tg and negative diagnostic (<sup>131</sup>I) whole body scan, treatment with high doses of (<sup>131</sup>I) may have

therapeutic utility in patients with lung metastases and, to a lesser extent, in those with lymph node metastases. However, in view of the frequent normalization of Tg values in untreated patients, we believe that treatment with (131)I should be considered according to the result of the first posttherapy scan. If positive in the lung, (131)I treatment should be continued up to total remission; surgical treatment should be preferred in patients with node metastases, and no treatment should be used in those with thyroid bed uptake or no uptake.

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## Nodular Goiter

- 13 -- Csako G, Byrd D, Wesley RA, Sarlis NJ, Skarulis MC, Nieman LK, Pucino F. Assessing the effects of thyroid suppression on benign solitary thyroid nodules. A model for using quantitative research synthesis. Medicine (Baltimore) 2000 Jan; 79(1): 9-26.**

Systematic review of the available information with a modified, largely quantitative method of research synthesis disclosed that an initial trial of thyroid hormone suppression therapy leads to clinically significant (> or = 50%) reduction of nodule size or arrest of nodule growth in a subset of patients with benign solitary thyroid nodules. In fact, in addition to objective improvements due to decreasing nodule size, L-T4 suppression therapy may benefit patients by reducing perinodular thyroid volume. Consequently, both pressure symptoms and cosmetic complaints may improve. (This objective review concludes that thyroid suppressive therapy is efficacious, a controversial point of view with which I agree.)

- 14 -- Wesche MF, Tiel-V Buul MM, Lips P, Smits NJ, Wiersinga WM. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. J Clin Endocrinol Metab 2001; 86:998-1005.**

The authors of this Dutch study randomized 32 patients with nontoxic nodular goiter to receive I-131 therapy and another 32 to receive thyroxine suppression, and followed them for 2 years. Their mean age was 50 years. The I-131 dose was 120 microcuries/ml and the initial T4 dose was 2.5 µg/kg. The T4 dose was adjusted to achieve a serum TSH between 0.01 and 0.1 mU/L. Mean thyroid volume was about 60 ml (17-260 ml). Goiter was decreased by 44% at 2 years in those receiving I-131. The response was inversely related to goiter size; the larger the goiter, the smaller the relative decrease in size. With levothyroxine therapy, there was not a significant decrease in goiter size for the group as a whole. However, 43% responded to T4 therapy with a decrease of 22% at two years. If patients who started with suppressed TSH were excluded, the response rate would have been 52% (11/21). The large suppressive T4 doses used caused a significant fall in BMD in the lumbar spine and hip. The authors conclude that I-131 therapy is more effective and better tolerated than levothyroxine suppression of TSH.

Mary Samuels wrote an interesting editorial about this study in which she summarized the 7 published studies of radioiodine therapy for sporadic nontoxic goiter :  
J Clin Endocrinol Metab. 2001 Mar;86(3):998-1005 Samuels MH. Evaluation and treatment of sporadic nontoxic goiter--some answers and more questions.

- 15 -- Stagnaro-Green A. Recognizing, understanding, and treating postpartum thyroiditis. Endocrinol Metab Clin North Am 2000 Jun; 29(2): 417-30, ix**

This is an excellent concise review of post-partum thyroiditis and its ramifications.

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## Subclinical Hyperthyroidism

- 16 -- **Bauer DC, Ettinger B, Nevitt MC, Stone KL**  
**Risk for fracture in women with low serum levels of thyroid-stimulating hormone.**  
**Ann Intern Med. 2001;134:561-8**

Women with TSH <0.1 mU/L, during an approximately 4-year followup, had a 3-fold increased risk for hip fracture and a 4-fold increased risk for vertebral fracture compared with women who had normal TSH.

- 17 -- **Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA.**  
**Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study.**  
**Lancet 2001 Sep 15; 358(9285): 861-5.**

Jayne Franklyn and her colleagues followed a cohort of 1191 people over age 60 who had been screened by serum TSH measurement. 71 (6%) had subnormal serum TSH, and 20 of these were <0.1 mU/L. During a 10 year follow-up, the mortality of those with subnormal TSH was 2.3-2.6-fold greater from circulatory and cardiovascular disease. This occurred at 2 to 5 years follow-up. To me, the results imply that subnormal TSH should be treated.

- 18 -- **Toft AD.**  
**Clinical practice. Subclinical hyperthyroidism.**  
**N Engl J Med. 2001;345:512-6. Review.**

Anthony Toft wrote an excellent review of this disorder. He recommends I-131 therapy for patients with subclinical hyperthyroidism and atrial fibrillation.

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## Graves' Eye Disease

- 19 -- **Bartalena L, Pinchera A, Marcocci C.**  
**Management of Graves' ophthalmopathy: reality and perspectives.**  
**Endocr Rev 2000 Apr;21(2):168-99**

This is a thorough review of the difficult problem of management of Graves' eye disease by the group which has done the best work in this area in the past decade.

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## Sodium Iodide Symporter

- 20 -- **Shen DH, Kloos RT, Mazzaferri EL, Jhiang SM.**  
**Sodium iodide symporter in health and disease.**  
**Thyroid 2001 May; 11(5): 415-25**

This an excellent review of the burgeoning literature on the sodium iodide symporter with a strong clinical emphasis.