

CLINICAL THYROIDOLOGY FOR PATIENTS



AMERICAN
THYROID
ASSOCIATION
FOUNDED 1923

VOLUME I • ISSUE I • AUGUST 2008

www.thyroid.org

- THYROID DIAGNOSIS** Lowering the thyrotropin reference limit to 2.5 μ IU/ml may result in inappropriate therapy for many euthyroid individuals. 1
- AUTOIMMUNE THYROID DISEASE** Autoimmune thyroid failure is higher than usual among thyroid antibody-positive individuals on an excessively high iodine diet 2
- NODULAR GOITER** Aggressive thyroid cancers may be missed in patients with multinodular goiter not undergoing periodic follow-up with neck ultrasonography 3
- THYROID NODULES** The likelihood of a radiation-induced thyroid nodule being malignant depends neither on its size nor number and biopsying only the largest nodule can miss up to half the thyroid cancers 4
- THYROID NODULES** Preoperative neck ultrasound examination accurately identifies most malignant nodules in patients with fine-needle aspiration cytology results that are suspicious for malignancy 5
- THYROID CANCER** PET/MRI fusion studies in patients with differentiated thyroid cancer. 6
- COMPLICATIONS OF RADIOIODINE THERAPY** There is a small risk of second primary nonthyroidal malignancies in patients with differentiated thyroid cancer . . . 7
- THYROID CANCER** This study compares the effect on tumor outcome after patients have been prepared for 131 I therapy using either thyroid hormone withdrawal or rhTSH preparation. 8
- THYROID CANCER** This is a study of papillary thyroid microcarcinoma, a tumor measuring 1 cm (0.4 in) or less in diameter, which has caused considerable debate regarding its diagnosis, treatment and long-term outcome. 9
- THYROID HORMONE THERAPY** Autoimmune atrophic gastritis may affect the intestinal absorption of levothyroxine. 10
- GRAVES' DISEASE** Radioiodine therapy for hyperthyroidism may have an effect on the eye component of Graves' disease. 11
- NONTHYROIDAL EFFECTS OF RADIOIODINE** The effect of radioiodine on the ovaries and offspring over a 10 year period 12
- GRAVES' DISEASE** Transient thyrotoxicosis may occur in patients with Graves' disease after withdrawal of antithyroid drug therapy. 13
- THYROTOXICOSIS** Hospitalization for arrhythmias and cardiovascular disease may be increased in patients with hyperthyroidism treated with radioiodine. 14
- THYROTOXICOSIS** Health status, mood and cognition in experimentally induced subclinical thyrotoxicosis. 15
- HYPERTHYROIDISM** More patients with TSH levels <0.05 mIU/L progress to overt hyperthyroidism than those with serum TSH levels ranging from 0.05 to 0.1 mIU/L. 16
- THYROID CANCER** Patients with large follicular thyroid cancers often develop T₃ toxicosis. However, T₃ is not commonly measured in patients with thyroid cancer. 17
- HYPOTHYROIDISM** Does levothyroxine (L-T₄) therapy restore serum T₃ levels in patients with hypothyroidism? 18
- HYPOTHYROIDISM** The diagnosis and management of subclinical hypothyroidism 19
- THYROID HORMONE THERAPY** Intestinal absorption of thyroid hormone may be impaired by drugs that impair gastric acid secretion. 20
- THYROID HORMONE THERAPY** Coffee interferes with the intestinal absorption of levothyroxine. 21
- THYROID AND ERECTILE DYSFUNCTION** Men with hyperthyroidism or hypothyroidism commonly have erectile dysfunction 22



AMERICAN
THYROID
ASSOCIATION

FOUNDED 1923

www.thyroid.org

Editor-in Chief

**Ernest L. Mazzaferri, MD,
MACP**

University of Florida
1600 SW Archer Road
PO Box 100226
Gainesville FL 32610-0226
Telephone: 352-392-2612
Fax: 352-846-2231
Email: thyroid@thyroid.org

Associate Editor

Jennifer A. Sipos, MD

Department of Medicine
Shands Hospital
1600 SW Archer Road
PO Box 100226
Gainesville FL 32610-0226
Telephone: 352-392-2612
Fax: 352-846-2231
Email: thyroid@thyroid.org

President

Rebecca S. Bahn, MD

President-Elect

Kenneth D. Burman, MD

Chief Operating Officer

Richard T. Kloos, MD

Treasurer

David H. Sarne, MD

Executive Director

Barbara R. Smith, CAE
American Thyroid Association
6066 Leesburg Pike, Suite 550
Falls Church, VA 22041
Telephone: 703-998-8890
Fax: 703-998-8893
Email: thyroid@thyroid.org

Designed by

Karen Durland
Email: kdurland@mindspring.com

Clinical Thyroidology for Patients

Copyright © 2008
American Thyroid Association, Inc.
Printed in the USA. All rights reserved.

CLINICAL THYROIDOLOGY **FOR PATIENTS**

A publication of the American Thyroid Association

VOLUME I • ISSUE I • AUGUST 2008

EDITOR'S COMMENTS

Clinical Thyroidology for Patients is a collection of summaries of recently published articles from the medical literature that covers the broad spectrum of thyroid disorders. A similar but more technical publication exists for physicians. This edition is written expressly for patients, although you are welcome to read the physician version which has considerably more technical information and is also available at the American Thyroid Association website at www.thyroid.org. Note that throughout the summaries there are links to abstracts in the literature and to websites that provide educational material that we think may be helpful. Simply click on the URL and the information will appear.

This is a service provided by the American Thyroid Association to help patients understand the complicated and often bewildering language of modern medicine. This publication is for informational purposes and is meant to serve as a link between patients and their physicians, to help bridge understanding of difficult and sometimes baffling thyroid problems. Knowledge is a powerful means of dealing with medical problems and we hope this journal will provide a source of strength and light that will assist you in making day-to-day decisions about your thyroid health.

Ernest L. Mazzaferri, MD, MACP

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 Table of 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.

[Back to Table of Contents](#)



THYROID DIAGNOSIS

WHAT IS THE STUDY ABOUT?

Lowering the thyrotropin reference limit to 2.5 μ IU/ml may result in inappropriate therapy for many euthyroid individuals.

THE FULL ARTICLE TITLE: “Thyrotropin levels in a population with no clinical, autoantibody or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism.” It is in the July 2008 issue of the *Journal of Clinical Endocrinology and Metabolism* (Volume 93 Issue 4, pages 1224-30). The authors are TE Hamilton, S Davis, L Onstad L, and KJ Kopecky.

http://www.ncbi.nlm.nih.gov/pubmed/18230665?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

The normal upper serum TSH limit has been debated. Some suggest that it should be lowered from approximately 4.0 to 2.5 μ IU/ml. This has major implications for the diagnosis and treatment of subclinical hypothyroidism, which could lead to millions of people worldwide being unnecessarily treated with thyroid hormone for a lifetime.

WHAT WAS THE AIM OF THE STUDY?

This study was aimed at identifying the normal upper serum TSH range in healthy people.

WHO WAS STUDIED?

The study was performed on 1861 individuals with no clinical evidence of thyroid disease who were randomly selected from the HDTS population for measurement of serum TSH levels and neck ultrasonography.

HOW WAS THE STUDY DONE?

Patients were divided into three normal reference groups that were selected with increasingly more stringent criteria to identify those without evidence of thyroid disease. TSH was retested by both older and contemporary laboratory methods.

WHAT WERE THE RESULTS OF THE STUDY?

The upper TSH reference limit was 4.1 μ IU/ml in the most rigorously screened individuals who had no clinical evidence of thyroid dysfunction.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

The results of this study were identical to the upper TSH limit of 4.12 μ IU/ml in the NHANES III study. Data from NHANES III is available at the following: <http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm>

WHAT ARE THE LIMITATIONS OF THIS STUDY?

One potential limitation is that no data were collected on family histories of thyroid disease.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Lowering the TSH reference limit to 2.5 μ IU/ml may result in inappropriate therapy for many individuals with normal thyroid function that is not likely to deteriorate in the future.

ABBREVIATIONS & DEFINITIONS

TSH Thyroid stimulating hormone (thyrotropin) is a pituitary hormone that stimulates the release of thyroid hormone from the thyroid gland. TSH levels increase when the thyroid gland fails to make sufficient thyroid hormone.

Reference Limit The upper normal limit of TSH above which doctors begin considering thyroid hormone therapy.

HDTS The Hanford Thyroid Disease study comprises people in the state of Washington who, during the 1940s and 1950s, were exposed as children to radioiodine (131 I) emissions from the Hanford nuclear facility and were considered to be at increased risk for thyroid disease. However, the study found no connection between 131 I exposure and thyroid disease.

Subclinical Hypothyroidism An asymptomatic condition in which patients have elevated serum TSH levels with normal serum thyroid hormone levels.

NHANES III is the third National Health and Nutrition Examination Survey. It can be found at: <http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm>

Web links are provided to provide further information.



AUTOIMMUNE THYROID DISEASE

WHAT IS THE STUDY ABOUT?

Autoimmune thyroid failure is higher than usual among thyroid antibody-positive individuals on an excessively high iodine diet

THE FULL ARTICLE TITLE: Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes.” It is in the February 2008 issue of the journal of *Clinical Endocrinology and Metabolism* (volume 93 Issue 5, pages 1751-57) The authors are Y Li, D Teng, Z Shan, X Teng, H Guan, X Yu, C Fan, W Chong, F Yang, H Dai H, X Gu, Y Yu, J Mao, D Zhao, JLi, Y Chen, R Yang C Li, W Teng.
http://www.ncbi.nlm.nih.gov/pubmed/18270254?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Blood levels of anti-thyroid antibodies correlate with the severity of chronic thyroid lymphocytic infiltration, which may cause thyroiditis, regardless of the presence or absence of hypothyroidism. However, the function and progression of these antibodies remains uncertain.

WHAT WAS THE AIM OF THE STUDY?

This study was aimed at identifying the natural progression of antithyroid antibodies and clinical hypothyroidism in areas with substantially differing iodine uptake.

WHO WAS STUDIED?

A total of 16,287 Individuals living in three rural areas in northern China with differing iodine intake (see Box) volunteered to undergo thyroid studies

How was the study done?

Baseline specimens were collected for urine iodine levels, serum TSH, TPOAb, and TgAb levels. In 2004, 80% of this group underwent follow-up studies using the same protocol except for the addition of neck ultrasound studies.

WHAT WERE THE RESULTS OF THE STUDY?

Initially, most subjects had normal thyroid function and only a few (~9%) had antibodies. The prevalence of antibodies was greater among women than among men and increased with age, especially in women. After 5 years, the rate of elevated TSH levels (>4.8 mIU/L) was higher

in those with anti-thyroid antibodies and was higher in areas of increased iodine intake: 5.3% in Panshan, 14.3% in Huanghua, and 23.4% in Huanghua (see Box).

HOW DOES THIS COMPARE WITH OTHER STUDIES?

These results confirm and add to those of the Whickham Survey, which also examined the natural history of individuals with baseline thyroid autoimmunity

WHAT ARE THE LIMITATIONS OF THIS STUDY?

There was a small loss of subjects when from the baseline to the follow-up study; however, the numbers were small and likely did not seriously affect the study

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Patients with anti-thyroid antibodies, especially women, develop thyroid failure more often than people without these antibodies. An excessive iodine intake also increases the risk for developing hypothyroidism.

ABBREVIATIONS & DEFINITIONS

TPOAb Serum anti-thyroid peroxidase antibodies

TgAb Anti-thyroglobulin antibodies

TSH Thyroid-stimulating hormone (thyrotropin)

Thyroiditis An inflammatory thyroid disorder that is affected by anti-thyroid antibodies that can lead to thyroid failure

Panshan A Chinese city with mild iodine deficiency.

Zhangwu A Chinese city with adequate iodine intake.

Huanghua A Chinese city with excessive iodine intake

U.S. Urinary Iodine Concentrations This is a reflection of iodine intake. Median urinary iodine level in 1971–74 was 320 and in 2000 has decline to 161 µg/L (NHANES III)
<http://www.cdc.gov/nchs/products/pubs/pubd/hestats/iodine.htm>



NODULAR GOITER

WHAT IS THE STUDY ABOUT?

Aggressive thyroid cancers may be missed in patients with multinodular goiter not undergoing periodic follow-up with neck ultrasonography.

THE FULL ARTICLE TITLE: "Fate of the non-operated, non-toxic goitre in a defined population." It is in the March 2008 issue of the *British Journal of Surgery* (volume 95 Issue 3 Pages 338-43). The authors are A Winbladh and J Järhult.

http://www.ncbi.nlm.nih.gov/pubmed/17929233?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum

WHAT IS THE PROBLEM BEING STUDIED?

This is a study of the medical effectiveness and hospital cost of a long-term "wait and see" follow-up strategy for patients with benign nodular goiter that had undergone fine-needle aspiration biopsy.

WHAT WAS THE AIM OF THE STUDY?

The study was undertaken to estimate the cost-effectiveness and risk of future significant thyroid disease in patients with benign non-toxic goiter after the initial clinical evaluation.

WHO WAS STUDIED?

The study patients were 261 of 587 individuals referred to a Swedish Surgical Department for consultation regarding nontoxic goiter. Neither goiter nor thyroid cancer is endemic in this area.

HOW WAS THE STUDY DONE?

Almost 90% of the patients had an FNAB, but none had a neck ultrasonography. The median duration of follow-up from the first diagnosis to telephone interview or second hospital referral was almost 11 years.

WHAT WERE THE RESULTS OF THE FOLLOW-UP STUDY?

In all, 46% of the patients were referred on a second occasion to the same hospital, mainly because of goiter enlargement or local symptoms, for which 48% had surgery. Most had benign goiter (77%), benign tumors or Hashimoto's thyroiditis, but a few (5%) had thyroid cancer. Five patients developed thyroid cancer during

follow-up; two died of anaplastic thyroid cancer almost 13 years after inclusion in the study and another died of an aggressive papillary thyroid cancer with brain metastases 7 years after a goiter had been diagnosed as benign. In-hospital cost of thyroid surgery for nodular goiter in Sweden is 3400€, and the authors' hospital saved 700 400€ over 15 years as a result of the policy of expectant waiting for patients with benign FNAB results.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

Two evidence-based reviews and the American Thyroid Association guidelines all recommend annual follow-up of patients with benign nodules or nodular goiter, with physical exam, neck ultrasonography, and serum TSH. Most cost-effectiveness studies include many patient and societal parameters in addition to direct costs. The guidelines and references for the above noted studies can be found on the internet at the following sites:

Thyroid nodule guidelines:

<http://www.thyroid.org/professionals/publications/documents/Guidelinsthy2006.pdf>

RESEARCH ARTICLES

http://www.ncbi.nlm.nih.gov/pubmed/18311576?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum

http://www.ncbi.nlm.nih.gov/pubmed/18311576?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum

<http://www.thyroid.org/professionals/publications/documents/Guidelinsthy2006.pdf>

WHAT ARE THE IMPLICATIONS OF THIS STUDY OF THIS STUDY?

Most patients with benign goiter should undergo yearly evaluations with serum TSH and neck ultrasonography.

ABBREVIATIONS & DEFINITIONS

FNAB Fine-needle aspiration biopsy is an out-patient method used to biopsy thyroid nodules with a very small needle, often under ultrasound guidance. Although this is the standard approach to the diagnosis of thyroid nodules, a few malignant nodules (~1%) yield benign cytology results, which are false-negative tests.



THYROID NODULES

WHAT IS THE STUDY ABOUT?

The likelihood of a radiation-induced thyroid nodule being malignant depends neither on its size nor number and biopsying only the largest nodule can miss up to half the thyroid cancers

THE FULL ARTICLE TITLE: “Size, number, and distribution of thyroid nodules and the risk of malignancy in radiation-exposed patients who underwent surgery.” It is in the April 2008 issue of the *Journal of Clinical Endocrinology and Metabolism* (volume 93, Issue 6, pages 2118-2193). The authors are DV Mihailescu and AB Schneider.
http://www.ncbi.nlm.nih.gov/pubmed/18381575?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

There are few studies to guide the selection of nodules for FNAB in patients exposed to radiation as children and young adults.

WHAT WAS THE AIM OF THE STUDY?

To evaluate how thyroid nodule size and number influence the risk of malignancy in patients exposed to radiation as children.

WHO WAS STUDIED?

To study the relationship between malignancy and nodule size, only nodules of known size were included, leaving 1998 nodules, 399 of which were malignant, in 1059 patients who had been exposed to irradiation before the age of 16 years for benign conditions of the head and neck and subsequently had surgery for thyroid nodules.

HOW WAS THE STUDY DONE?

The size, location and diagnosis of malignant nodules were determined from the pathology report. The rank order of the largest malignant nodule compared with the rest of the patient’s nodules was used to calculate how many cancers would have been missed if the nodule size were the only factor used to determine the need for FNAB.

WHAT WERE THE RESULTS OF THE STUDY?

There was no increase in the risk of malignancy with increasing nodule size and the risk of malignancy in a

nodule was similar with solitary (19%) and multiple (17%) nodules. Still, thyroid cancer was found in fewer patients (19%) with solitary nodules than patients with multiple nodules (31%). Performing FNAB on only the largest nodules would have missed 42% of the 264 thyroid cancers. If only the two largest nodules had been biopsied, 45 cases of thyroid cancer (17%) would have been missed.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

Although the risk of malignancy in nodules of non-irradiated patients is generally greater with larger nodules, some studies suggest this is different in irradiated patients. This study is in accord with the American Thyroid Association guidelines on thyroid cancer and nodules that is available at no cost at the following website:
<http://www.thyroid.org/professionals/publications/documents/Guidelinsthy2006.pdf>

WHAT ARE THE LIMITATIONS OF THIS STUDY?

Before 1993 surgery was performed on the basis of physical examination that disclosed thyroid nodular disease. Also, the size and location of thyroid nodules was not available on all patients.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study has five major findings:

- The likelihood of a radiation-induced nodule being malignant depends neither on its size nor presence of other thyroid nodules.
- The risk for thyroid cancer increases when a radiation-exposed patient has more than one thyroid nodule.
- Performing FNAB on only the two largest nodules would miss a significant number of malignant tumors and nodules smaller than 1 cm (0.4 inch) in diameter should be biopsied.
- Over half of the patients with thyroid cancer had multiple tumors that involved both thyroid lobes.
- There is an inverse relationship between the number of malignant and benign nodules, but why this occurs is uncertain.

ABBREVIATIONS & DEFINITIONS

FNAB fine-needle aspiration biopsy



THYROID NODULES

WHAT IS THE STUDY ABOUT?

Preoperative neck ultrasound examination accurately identifies most malignant nodules in patients with fine-needle aspiration cytology results that are suspicious for malignancy

THE FULL ARTICLE TITLE: “Role of ultrasound in thyroid nodules with a cytology reading of suspicious for papillary thyroid carcinoma.” It is in the April Issue of *Thyroid* (Volume 18 Issue 5 pages 517-22.) The authors are JY Kwak, EK Kim, MJ Kim, SW Hong, SH Choi, EJ Son, KK Oh, CS Park, WY Chung, and KW Kim. To view the abstract of this article see:

<http://www.ncbi.nlm.nih.gov/pubmed/18407756?dopt=Citation>

WHAT IS THE PROBLEM BEING STUDIED?

Malignancy is found in up to 80% of FNAB cytology specimens interpreted as suspicious for papillary thyroid cancer. Current guidelines suggest that patients with this finding should undergo surgery but it is possible that neck ultrasound might identify the few patients with benign tumors, thus avoiding unnecessary surgery.

WHAT WAS THE AIM OF THE STUDY?

To investigate the role of ultrasound in nodules with suspicious cytology on FNAB

WHO WAS STUDIED?

303 patients with 10,497 thyroid nodules who had neck ultrasound and FNAB

HOW WAS THE STUDY DONE?

Ultrasound was performed by three radiologists with extensive thyroid ultrasound experience who also performed the ultrasound-guided-FNAB. Each nodule was determined to be either ultrasonographically consistent with malignancy or probably benign.

WHAT WERE THE RESULTS OF THE STUDY?

The diagnostic sensitivity of ultrasound in identifying malignant nodules was 96%, the specificity was 75%, the PPV was 95% and the NPV was 81%, and overall accuracy was 93%. (See Box)

HOW DOES THIS COMPARE WITH OTHER STUDIES?

A few studies report that about 80% of nodules yielding cytology that is suspicious for papillary thyroid carcinoma are found at surgery to be papillary thyroid cancers. Still, the studies

are small and frequently mix several types of thyroid cancers, making the interpretation of the findings difficult. This study involved only ultrasound-guided FNAB after the ultrasound diagnosis had been established.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

The ultrasound examinations were done by three very experienced radiologists who performed the ultrasound-guided FNAB after the ultrasound diagnosis had been established, which may have played a role in increasing the accuracy of the cytology findings. A greater number of biopsies may have been done on nodules that appeared ultrasonographically malignant. An ultrasound examination done in the hands of less experienced ultrasonographers would yield less accurate information.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The American Thyroid Association cancer guidelines advise either lobectomy or total thyroidectomy if a thyroid nodule yields cytology that is suspicious for papillary cancer. Even with excellent ultrasonographers, there is a small risk (~4%) of missing a diagnosis of thyroid cancer when the FNAB cytology is positive. One must know this risk when opting to forgo surgery when the cytology diagnosis is suspicious for papillary thyroid cancer and the ultrasound exam is negative.

To review the American Thyroid Association guidelines see: <http://www.thyroid.org/professionals/publications/documents/Guidelinesthy2006.pdf>

ABBREVIATIONS & DEFINITIONS

FNAB fine-needle aspiration biopsy

Sensitivity is the probability of a positive test among patients with disease

Specificity is the probability of a negative test among patients without disease

Positive Predictive Value (PPV) is the proportion of patients with positive test results who have tumor

Negative predictive value (NPV) is the proportion of patients with a negative test who do not have tumor



THYROID CANCER

WHAT IS THE STUDY ABOUT?

PET/MRI fusion studies in patients with differentiated thyroid cancer.

THE FULL ARTICLE TITLE: “Utility of PET/neck MRI digital fusion images in the management of recurrent or persistent thyroid cancer” It is in the February 2008 issue of *Thyroid* (Volume 18, Issue 2, pages 103-11. The authors are L Seiboth, D Van Nostrand, L Wartofsky, L., Y Ousman, J Jonklaas, C Butler, F Atkins, and K Burman. http://www.ncbi.nlm.nih.gov/pubmed/18279011?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Serum thyroglobulin levels and neck ultrasound examinations are the mainstay of diagnostic follow-up studies in patients who clinically appear free of disease. Patients with more serious disease usually require a variety of imaging studies to identify the site and extent of metastatic tumor. One such study is PET scanning that is being increasingly utilized with CT or MRI to produce images that provide both anatomic and metabolic information.

WHAT WAS THE AIM OF THE STUDY?

To assess the clinical utility of coregistered (fused images) of PET and MRI in patients with thyroid cancer

WHO WAS STUDIED?

The study subjects were 34 patients with thyroid cancer who had undergone PET and MRI imaging for thyroid cancer at some point during their follow-up. Of this group, 31 (91%) had papillary thyroid cancer and one had medullary thyroid cancer. All were initially treated with total or near-total thyroidectomy.

HOW WAS THE STUDY DONE?

Four endocrinologists who did not know the results of the fusion studies each reviewed the patient charts to make a clinical assessment and theoretical treatment plan. After this was accomplished, each endocrinologist was individually provided the results of the PET/MRI studies. With these new images, each endocrinologist made a revised clinical assessment and treatment plan and then categorized the PET/MRI information into three groups: (1) new information that altered the treatment plan, (2) new information that confirmed the initial proposed treatment plan, or (3) no new information.

WHAT WERE THE RESULTS OF THE STUDY?

The PET/MRI fusion studies provided additional information that altered the treatment plan in 46% of the patients, and confirmed the proposed treatment plan in 36% patients and provided no additional information in 18% of the patients.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

There no similar studies with which to compare this study.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

The main limitation is that PET/MRI was not compared with PET/CT, the most commonly used digitally fused PET studies.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study provides important information that may change decisions regarding surgical therapy for patients with thyroid cancer. This requires further study.

ABBREVIATIONS & DEFINITIONS

PET Positron Emission Tomography is a scanning technique used in conjunction with small amounts of radiolabeled glucose to visualize the anatomy and function of tumors, including information on blood flow, glucose metabolism and tumor location.

PET/CT PET scans alone often do not identify the precise anatomical location of a tumor. To fix this, radiologists digitally fuse the PET scan and a Computed tomography (CT) into one image which provides both functional and anatomical information about a tumor. Other imaging devices can also be fused with PET scans.

MRI/PET MRI is magnetic resonance imaging, a procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed images of areas inside the body. MRI produces better images of organs and soft tissue than many other scanning techniques, such as computed tomography (CT) or x-ray. MRI is especially useful for imaging the brain, spine, and soft tissue of joints, and the inside of bones. The National Cancer Institute website has considerable information on these imaging devices.

http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=45997

<http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm>



COMPLICATIONS OF RADIOIODINE THERAPY

WHAT IS THE STUDY ABOUT?

There is a small risk of second primary nonthyroidal malignancies in patients with differentiated thyroid cancer

THE FULL ARTICLE TITLE: “The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer.” It is in the February 2008 issue of the *Journal of Clinical Endocrinology and Metabolism*, (volume 93 Issue 2, pages 504-15) The authors are AP Brown, J Chen, YJ Hitchcock, A Szabo, DC Shrieve, and JDT Ward. http://www.ncbi.nlm.nih.gov/pubmed/18029468?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Papillary and follicular thyroid cancers are common in young and middle-aged adults and are associated with cancer-specific survival rates that exceed 90%. Because they are typically treated with total thyroidectomy and often with radioiodine postoperatively, studies raise concerns about the risk of second non-thyroid malignancies.

WHAT WAS THE AIM OF THE STUDY?

This study was done to identify the risk of second cancers in patients treated with radioactive iodine.

WHO WAS STUDIED?

The study subjects were 26,517 patients with papillary and 3761 with follicular thyroid cancer treated between 1973 and 2002; 76% were female, and 24% were male. Median age was 43 years at the time of diagnosis.

HOW WAS THE STUDY DONE?

Information was obtained from the U.S. National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program that has the largest cancer database in the world with the longest period of follow-up. The risk of second cancers in patients with thyroid cancer was compared with cancers among persons in the general population matched for age, gender and calendar periods of study (control group).

WHAT WERE THE RESULTS OF THE STUDY?

Between 1973 and 2002, 2158 thyroid cancer patients had 2338 second malignancies of almost all types. The risk was greatest for patients aged 25 to 29 years and for a period of 5 years after diagnosis of thyroid cancer, after which it declined rapidly and remained low. Compared with the

general population, there was an excess risk for some but not all cancers. An analysis of patients treated between 1988 and 2002, when information concerning radioiodine was available, found the risk of second malignancies was significantly greater in the radioisotope-treated group than in the general population.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

Elevated risk of second primary malignancies among thyroid cancer survivors have been found in numerous studies in the past 10 years. An analysis of 13 such studies found a 20% increase in cancer risk among patients with thyroid cancer as compared with the general population. However, a study from the Netherlands found that disease-free patients who were treated for thyroid cancer achieved a normal life span in contrast to patients with persistent thyroid cancer who had a median life-expectancy of only 60% predicted for their age. The study concluded that overall, treatment including radioiodine is safe.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

This and most other studies fail to describe how much radioiodine is necessary to cause second primary malignancies. However, a study from France found a linear relationship between the cumulative exposure to radioiodine and the risk of solid cancers and leukemia. The study found that one might expect 172 excess cancers per 10,000 people surviving 20 years after treatment of thyroid cancer with the mean of 163 mCi of radioiodine. The amount of radioiodine given postoperatively to destroy occult thyroid cancer and the normal thyroid remnant is usually 30 to 100 mCi, while larger doses are usually given only when thyroid cancer metastases are found.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

There is a small but not inconsequential increased risk of second cancers in patients with thyroid cancer treated with and without radioiodine. The risk of breast cancer is increased in patients not treated with radioiodine, whereas certain types of leukemia and lymphatic tumors and stomach cancer are increased in patients treated with radioiodine. Patients with thyroid cancer should thus undergo routine screening measures as recommended by the U.S. Public Health Service.

Details of informed decision-making to promote cancer screening are available on the website for the Center for Disease Control

<http://www.thecommunityguide.org/cancer/idm/>



THYROID CANCER

WHAT IS THE STUDY ABOUT?

This study compares the effect on tumor outcome after patients have been prepared for ¹³¹I therapy using either thyroid hormone withdrawal or rhTSH preparation.

THE FULL ARTICLE TITLE: “Recombinant Human TSH-Assisted Radioactive Iodine Remnant Ablation Achieves Short-Term Clinical Recurrence Rates Similar to Those of Traditional Thyroid Hormone Withdrawal” It is in the *Journal of Nuclear Medicine* published in May 2008. (Volume 49, Issue 5, pages 764-70). The authors are RM Tuttle, M Brokhin, G Omry, AJ Martorella, SERUM Larson, RK Grewal, M Fleisher, RJ Robbins. The abstract can be obtained at: http://www.ncbi.nlm.nih.gov/pubmed/18413378?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed-ResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Patients with differentiated thyroid carcinoma require high serum TSH levels before radioiodine can be given for diagnostic or therapeutic purposes. The serum TSH can be increased by stopping thyroid hormone or by injecting rhTSH. Although many studies show that rhTSH is as effective as thyroid hormone withdrawal (hypothyroidism) for preparing patients, there are no published studies comparing the clinical outcome when rhTSH or thyroid hormone withdrawal is used to prepare patients for thyroid remnant ablation.

WHAT WAS THE AIM OF THE STUDY?

To compare the therapeutic effectiveness of ¹³¹I in patients prepared with thyroid hormone withdrawal compared with rhTSH.

WHO WAS STUDIED?

In all, 394 patients with thyroid cancer were studied; 74 underwent thyroid withdrawal and 320 were given rhTSH. Patients in the rhTSH group were significantly older than those in the withdrawal group (median age 46.5 years; range 18 to 83 vs. 44.0; range 6 to 81) but there were no other important differences in the two groups of patients and their tumors.

HOW WAS THE STUDY DONE?

Patients were treated with 75 to 100 mCi of ¹³¹I and evaluated at 6, 12 and 18 months after surgery and ¹³¹I therapy and underwent an assessment of remnant ablation a median of 29 months after ¹³¹I therapy.

WHAT WERE THE RESULTS OF THE STUDY?

The rhTSH group was slightly but significantly more likely than the thyroid hormone withdrawal group to have no evidence of disease (76% vs. 62%), and the rhTSH was less likely to have persistent disease than the withdrawal group (16% vs. 24%, P=0.1) Using slightly more rigorous criteria, patients in the rhTSH group were significantly more likely than the thyroid hormone withdrawal group to have no evidence of disease (19% vs. 32%).

HOW DOES THIS COMPARE WITH OTHER STUDIES?

This is the only study to compare clinical outcomes measured in terms of tumor persistence or recurrence compared with surrogate tumor markers alone such as serum thyroglobulin levels.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

Because this is a retrospective study, there may be patient selection bias. For instance, the older age of patients prepared with rhTSH should bias this group towards a poorer outcome, but the rhTSH group had a significantly better outcome than the thyroid hormone withdrawal group suggesting that rhTSH is even better than found in this study.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This is the first study to clearly show that the therapeutic effect using rhTSH is at least comparable to preparing patients with thyroid hormone withdrawal.

ABBREVIATIONS & DEFINITIONS

Recombinant human TSH (rhTSH) is an injectable form of thyrotropin (TSH, thyroid stimulating hormone) which is used in patients with differentiated thyroid cancer (papillary, follicular and Hürthle cell thyroid cancer). The drug has been approved for both diagnostic use and for preparing patients for radioiodine (¹³¹I) therapy to destroy any remaining thyroid tissue that persists after total or near-total thyroidectomy (remnant ablation), which facilitates follow-up and lowers recurrence rates in most patients. Studies show that the drug is therapeutically comparable to thyroid hormone withdrawal without producing symptoms of hypothyroidism (patients continue taking thyroid hormone with rhTSH). Also, rhTSH imparts 33% less whole-body radiation from ¹³¹I than occurs with thyroid hormone withdrawal.



THYROID CANCER

WHAT IS THE STUDY ABOUT?

This is a study of papillary thyroid microcarcinoma, a tumor measuring 1 cm (0.4 in) or less in diameter, which has caused considerable debate regarding its diagnosis, treatment and long-term outcome.

THE FULL ARTICLE TITLE: “Papillary microcarcinoma”

It is in the May 2008 issue of *World Journal of Surgery* (Volume 32, Issue 5, pages 747-53. The authors are S Noguchi, H Yamashita., S Uchino, S Watanabe.

http://www.ncbi.nlm.nih.gov/pubmed/18264828?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Although papillary thyroid microcarcinomas comprise almost half of the thyroid cancers diagnosed in the United States and Europe, there is debate regarding their management. Although long-term survival rates are in the range of 99%, a small but important number of patients develop metastasize and some have tumors invade the esophagus and nerves in the neck. Some have suggested this tumor requires no therapy.

WHAT WAS THE AIM OF THE STUDY?

This large retrospective study was done to better understand the management of papillary microcarcinoma.

WHO WAS STUDIED?

In all, 2070 patients with papillary microcarcinoma were studied among 4840 patients (43%) with papillary thyroid cancer, all of whom were treated with total or near-total thyroidectomy. Their median age at the time of surgery was 47 years (range, 11 to 83), and the male-to-female ratio was 1:8.9.

HOW WAS THE STUDY DONE?

Patients were all treated and underwent follow-up at the Noguchi Thyroid Clinic and Hospital Foundation in Japan, where the authors perform over 1500 thyroid operations annually. The authors have been gathering follow-up data on thyroid cancer patients since 1922.

WHAT WERE THE RESULTS OF THE STUDY?

Although only 12% of the patients had lymph node metastases removed from the central part of the neck, about half of them were malignant. In all, only 3.5% of

the patients experienced a recurrence after a median of 10.3 years, but the 30-year recurrence rate was 40% in patients older than 55 years and less than 10% in patients younger than 55 years. Recurrence rates after 35 years of follow-up were 3% and 14% for tumors 1 to 5 mm and 6 to 10 mm, respectively. Almost all of the recurrences were in the neck. Of 2070 patients who underwent follow-up for 16.5 ± 7.3 years, only 12 (0.6%) died of thyroid cancer. When the primary tumor adheres to or invades the recurrent laryngeal nerve, which controls the vocal cords, or the muscular layer of the esophagus, recurrence-free survival rate decreased significantly.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

There no other studies of this magnitude and such large long-term follow-up.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

Radioiodine therapy was not given to the patients in this study, and thus no information is available on this point.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Patients with papillary microcarcinoma older than 55 years have high tumor recurrence rates but low cancer-specific mortality rates. This tumor is similar to larger papillary thyroid cancers in which age-based recurrence rates extend for many years justifying long-term follow-up with neck ultrasonography.

The American Thyroid Association guidelines suggest total thyroidectomy for papillary microcarcinoma that is diagnosed preoperatively and for tumors that are metastatic or invasive.

<http://www.thyroid.org/professionals/publications/documents/Guidelinesthy2006.pdf>

ABBREVIATIONS & DEFINITIONS

Papillary microcarcinoma is a form of papillary thyroid cancer that is 1 cm (0.4 in) or smaller in diameter. However, this small tumor accounts for almost half of the thyroid cancers diagnosed in the past three decades. There are often multiple papillary microcarcinomas in the thyroid gland and up to 50% develop lymph-node metastases in the central and lateral areas of the neck. However, the 10-year mortality rates in patients with this tumor are in less than 1 %. Some patients develop invasive disease in the neck.



THYROID HORMONE THERAPY

WHAT IS THE STUDY ABOUT?

Autoimmune atrophic gastritis may affect the intestinal absorption of levothyroxine.

THE FULL ARTICLE TITLE: “L-thyroxine requirement in patients with autoimmune hypothyroidism and parietal cell antibodies” It is in the February 2008 issue of the *Journal of Clinical Endocrinology & Metabolism* (Volume 93, Issue 2, pages 465-69. The authors are S Checchi, A Montanaro, L Pasqui, C Ciuoli, V De Palo, MC Chiappetta, and F Pacini. The abstract can be obtained from: <http://www.ncbi.nlm.nih.gov/pubmed/18042648?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Based on the frequent association of parietal-cell antibodies (PCAs) with atrophic gastritis and autoimmune thyroid disease, the authors of this study hypothesized that PCA-positive patients may require higher than usual doses of L-T₄ and that this may be another cause for increased daily L-T₄ requirements

WHAT WAS THE AIM OF THE STUDY?

The study was designed to find a relationship between the daily dose of L-T₄ and the presence of autoimmune gastritis.

WHO WAS STUDIED?

The study subjects were 391 patients taking L-T₄ for mild autoimmune hypothyroidism. None had stomach disorders or were taking drugs known to affect L-T₄ intestinal absorption. In addition 60 patients who had undergone thyroid surgery for Graves’ disease or multinodular goiter were studied to compare their results the study group results.

HOW WAS THE STUDY DONE?

Nearly 50% of the patients agreed to undergo stomach biopsy to be examined for atrophic gastritis. Blood was tested for PCA and serum TSH (thyroid stimulating hormone) levels to provide a measurement of the adequacy of L-T₄ replacement.

WHAT WERE THE RESULTS OF THE STUDY?

The daily L-T₄ requirements increased by 17% when parietal cell antibodies were present and 26% when gastric atrophy was present, and increased by 55% when gastric atrophy went from mild to severe.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

Most but not all studies find that reduced gastric acid secretion impairs L-T₄ absorption, perhaps because it is not always associated with severe gastric parietal cell atrophy.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

There are no serious limitations to this study.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The observations in this study suggest that serum parietal-cell antibody levels might be measured when the response to thyroxine therapy fails to achieve the expected goals

ABBREVIATIONS & DEFINITIONS

Levothyroxine (L-T₄) is the usual oral form of thyroid hormone that is administered to patients for the treatment of hypothyroidism (thyroid failure) or for the treatment of thyroid cancer when the drug is administered to suppress serum thyrotropin (TSH, thyroid-stimulating hormone) levels. It should be taken on an empty stomach, usually in the morning about an hour after breakfast, although it may be taken before sleep if food has not been ingested for the past hour.

Many things interfere with L-T₄ therapy, including compliance (taking the drug as directed), reduced absorption from gastrointestinal disorders such as stomach or duodenal ulcers, malabsorption, liver disease, medications such as iron supplements, antacids, resins, lovastatin (a cholesterol lowering drug), sucralfate (an antacid), calcium carbonate, soybeans, coffee, high-fiber diet, and many other things, such as impaired stomach acid secretion.

Parietal Cells These cells line the stomach wall and produce gastric acid that seems necessary for L-T₄ absorption. Patients may develop anti-parietal cell PCA anti-parietal cell antibodies

Autoimmune Thyroid Disease (Hashimoto’s thyroiditis) is a form of thyroiditis that is a frequent cause of hypothyroidism.

Internet information: the link below provides a good source of patient information on this subject:

<http://www.uptodateonline.com/patients/index.html>



GRAVES' DISEASE

WHAT IS THE STUDY ABOUT?

Radioiodine therapy for hyperthyroidism may have an effect on the eye component of Graves' disease.

THE FULL ARTICLE TITLE: "Radioiodine therapy and Graves' ophthalmopathy" It is in the June 2008 issue of the *Journal of Nuclear Medicine* (Volume 49, Issue 6, pages 923-30). The authors are JC Sisson, M Schipper, CC Nelson, JE Freitas, and BR Frueh. The abstract can be obtained from: http://www.ncbi.nlm.nih.gov/pubmed/18483104?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed.ResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

The available randomized, controlled trials on the effects of radioiodine (¹³¹I) therapy on Graves' ophthalmopathy (GO), which have been done mainly in Europe, show that about 15% of patients have new eye disease or progression of preexisting GO within 6 months after the administration of ¹³¹I.

WHAT WAS THE AIM OF THE STUDY?

This study explores the effects, if any, on the of American patients with Graves' disease treated with ¹³¹I

WHO WAS STUDIED?

The study subjects were 76 patients with Graves' disease, ranging in age from 10.6 to 72 years, of whom 61 (85%) were female. All had ¹³¹I therapy for Graves' hyperthyroidism.

HOW WAS THE STUDY DONE?

During follow-up evaluations at 2, 6, and 12 to 14 months after therapy, thyroid-function tests, thyroid stimulating hormone (TSH) measurements, and data from ophthalmologists and ophthalmic technicians were obtained to fulfill the 10 items of the clinical activity score (CAS), which is a standard means of evaluating the clinical degree of GO.

WHAT WERE THE RESULTS OF THE STUDY?

The mean exophthalmometer readings increased 2 mm or more but the changes were not statistically significant and spontaneously return to normal 1 year after ¹³¹I therapy.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

The few randomized, prospective studies examining the potential impact of radioiodine therapy on GO found that approximately 15% of European patients have new eye disease or experience progression related to the treatment within 6 months. Still, the progression is mild and persists at 1 year in only 5%. The risk is greatest in patients with active GO treated with radioiodine

and is almost eliminated by giving a short course of oral glucocorticoids and avoiding posttreatment hypothyroidism. Smokers are at increased risk of developing sever GO.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

This study has several important limitations. This is an unselected population and the study had an unusual use of the CAS system, grouping the patients results, rather than using individual observations, making it difficult to ascertain exactly how many of the patients had evidence of GO at baseline, and whether their disease was active.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study does not provide strong support for the notion that American patients do not develop GO after treatment with ¹³¹I. It is likely that the careful European studies of this subject provide information that is applicable to patients in the United States. <http://www.ncbi.nlm.nih.gov/pubmed/18299459?dopt=Citation>

ABBREVIATIONS & DEFINITIONS

Graves's disease This is the commonest cause of hyperthyroidism (overactive thyroid). It is characterized by goiter, exophthalmos (Graves' ophthalmopathy) and hyperthyroidism that is mediated by an autoimmune antibody-mediated stimulation of the thyroid gland.

GO is Graves' ophthalmopathy

The characteristic features of Graves' eye disease are symptoms of inflammation of the eye tissues. The eyes are painful, red and watery and the covering of the eye is inflamed and swollen. The lids and tissues around the eyes are swollen. The eyeballs bulge out of their sockets, and because of eye muscle movement, the eyes may be unable to move normally and there may be blurred or double vision. On examination, the degree to which the eyes are pushed out of their sockets can be measured using an instrument called an "exophthalmometer."

CAS is the clinical activity score that provides a guide in the management of patients with Graves' ophthalmopathy. The original description of CAS is found at: <http://www.ncbi.nlm.nih.gov/pubmed/9302365?dopt=Citation>

Examples of ophthalmopathy can be found at: <http://en.wikipedia.org/wiki/Exophthalmos>



NONTHYROIDAL EFFECTS OF RADIOIODINE

WHAT IS THE STUDY ABOUT?

The effect of radioiodine on the ovaries and offspring over a 10 year period

THE FULL ARTICLE TITLE: “Therapeutic Administration of ¹³¹I for Differentiated thyroid cancer: radiation dose to ovaries and outcome of pregnancies” It is in the May 2008 issue of the *Journal of Nuclear Medicine* (Volume 18, Issue 59, pages 854-52. The authors are JP Garsi, M Schlumberger, C Rubino, M Ricard, M Labbe, C Ceccarelli, C Schvartz, M Henri-Amar, S Bardet, and F De Vathaire, F.
http://www.ncbi.nlm.nih.gov/pubmed/18413399?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed-ResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Ten years ago this group reported that radioiodine (¹³¹I) therapy for thyroid cancer had no effects on the outcome of subsequent pregnancies and offspring in women treated for thyroid cancer, with the exception of miscarriages in a small number of women that occurred during the first year after ¹³¹I therapy.

WHAT WAS THE AIM OF THE STUDY?

The study was designed to assess the rate of induced abortions, miscarriage, stillbirth, prematurity, birth weight below the 10th percentile for gestational age, congenital abnormalities, and death during the child’s first year of life and the development of thyroid disease in children, including tumors at other sites.

WHO WAS STUDIED?

Study subjects were 1126 women with differentiated thyroid cancer who had a total of 2078 pregnancies. In this group, 44% were given 100 mCi or more of ¹³¹I in 1 to 11 treatments that were administered a mean of 35 months (range, 0 to 243) before conception.

HOW WAS THE STUDY DONE?

From 1994 to 2004 all the women treated for thyroid cancer at the Institut Gustave-Roussy in Paris and the Institut Jean Godinot in France and at the Institute of Endocrinology in Pisa were routinely interviewed by trained data managers, who collected information regarding the following features of each pregnancy.

WHAT WERE THE RESULTS OF THE STUDY?

A total of 341 therapeutic and elective abortions were done, 65% before treatment, and 8% after thyroid cancer surgery alone, and 28% after both surgery and ¹³¹I therapy. Induced

abortions were more frequent after surgical therapy, both with and without ¹³¹I therapy, than before any treatment had been done. Higher cumulative amounts of ¹³¹I (10 to 100 mCi) before pregnancy were not associated with a greater probability of an induced abortion. A total of 18 induced abortions of 34 pregnancies occurred in women who had received ≥ 10 mCi ¹³¹I during the year before conception, which was a greater proportion of abortions than occurred in pregnancies preceded by smaller amounts of ¹³¹I.

Miscarriages were observed in 193 of 1857 pregnancies (10%) before any thyroid cancer treatment was administered, and were more frequent (21%) in pregnancies that occurred after surgery alone, but were about the same before (20%) and after (19%) ¹³¹I therapy. There was no correlation between the cumulative amount of ¹³¹I therapy of and the occurrence of miscarriage.

Among the 2009 live births, none of the following appeared to be modified by mother’s previous surgery or ¹³¹I exposure: prematurity, low birth weight, death before 1 year, malformation, thyroid disease, and cancers. In all, 1.3% of 1633 died less than 37 weeks after birth, 22 were before mothers were given treatment and 3 after the mother’s surgery for thyroid cancer

HOW DOES THIS COMPARE WITH OTHER STUDIES?

This is the largest study of patients with the longest follow-up of the published literature.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

The main limitation of the study is that fetal malformations and loss were not compared to the general population in France and Italy because the two countries coded these two outcomes differently.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Radioiodine therapy for women with thyroid cancer does not adversely affect subsequent pregnancies and offspring over a 10-year follow-up period. There was no correlation between the cumulative amount of ¹³¹I therapy of and the occurrence of miscarriage.

ABBREVIATIONS & DEFINITIONS

Radioiodine (¹³¹I) is used to treat papillary follicular and Hürthle cell cancer (differentiated thyroid cancer). appo 30 to 100 mCi of ¹³¹I is used for thyroid remnant ablation to destroy residual thyroid tissue and to facilitate follow-up of patients with thyroglobulin and whole body radioiodine scans. Patients with metastases are treated with approximately 100 to 200 mCi.



GRAVES' DISEASE

WHAT IS THE STUDY ABOUT?

Transient thyrotoxicosis may occur in patients with Graves' disease after withdrawal of antithyroid drug therapy.

THE FULL ARTICLE TITLE: "The prevalence of transient thyrotoxicosis after antithyroid drug therapy in patients with graves' disease" It is in the January 2008 issue of *Thyroid* (Volume 18, Issue 1, pages 63-6. The authors are S Kubota, K Takata, T Arishima, H Ohye, E Nishihara, E. Thyroid Kudo, M Ito, S Fukata, N Amino, and A Miyauchi, A.
http://www.ncbi.nlm.nih.gov/pubmed/18302519?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Transient thyrotoxicosis sometimes occurs in patients with Graves' disease after withdrawal of antithyroid drugs, but the prevalence of this phenomenon is unknown. However, when it occurs, patients may receive unnecessary therapy.

WHAT WAS THE AIM OF THE STUDY?

This study was done to assess the prevalence and duration of transient thyrotoxicosis after withdrawal of antithyroid drugs.

WHO WAS STUDIED?

Study subjects were 110 patients with Graves' disease whose antithyroid drug therapy was stopped after their thyrotoxicosis went into remission. In all, 94 (85%) were female, and the mean age was 38 years. Patients were treated with antithyroid drugs (methimazole or propylthiouracil) for an average of 43 months.

HOW WAS THE STUDY DONE?

Antithyroid drugs were discontinued when the following were observed: small goiter, low levels (<30%) of immunoglobulin inhibitor (TBII) and a serum thyrotropin (TSH) of 0.3 to 5.0 mIU/L and serum free thyroxine (FT₄) of 0.7 to 1.6 ng/dl for more than 6 months with the lowest doses of antithyroid drugs.

WHAT WERE THE RESULTS OF THE STUDY?

Of 110 patients, 62% had a remission. In all, 41% had transient thyrotoxicosis and 59% had remission without thyrotoxicosis. Twenty-eight patients became euthyroid after transient thyrotoxicosis, and 8 of 28 patients showed overt thyrotoxicosis while the rest had subclinical thyrotoxicosis.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

There no similar studies with which to compare this study.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

The main limitation is that patients were treated in one institution where the physicians were carefully studying this problem, which may not happen in day-to-day practice.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

After antithyroid drug withdrawal, nearly half the relapses of Graves' hyperthyroidism are transient and require no further therapy. The majority of transient relapses occurs 3 to 6 months after the withdrawal of antithyroid drugs and persists for an average of 7 months but can last longer. This may be a problem for older patients but for the rest one should assess the patient at monthly intervals without therapy to avoid unnecessary treatment.

ABBREVIATIONS & DEFINITIONS

Graves's Disease This is the most common cause of hyperthyroidism (overactive thyroid). It is characterized by goiter, exophthalmos (Graves' ophthalmopathy) and hyperthyroidism that is mediated by an autoimmune antibody-mediated stimulation of the thyroid gland. Hyperthyroidism is treated with radioiodine, antithyroid drugs or surgery. Each has benefits and shortcomings but most adults in the US with Graves' disease hyperthyroidism are treated with radioiodine. Still, many patients opt for antithyroid drugs.

Relapse of Thyrotoxicosis with Antithyroid Drugs The relapse rate of hyperthyroidism following the withdrawal of antithyroid drugs in patients with Graves' disease is generally about 30% to 50% but no laboratory tests or clinical features, including longer duration of antithyroid drug therapy or addition of levothyroxine (thyroid hormone) fail to accurately predict permanent remission of thyrotoxicosis.

TSH pituitary thyrotropin (Thyroid Stimulating Hormone)

TSI Thyroid stimulating-immunoglobulin that stimulates the synthesis and release of thyroid hormones

TBII Thyroid-binding immunoglobulin that inhibits the synthesis and release of thyroid hormones.

TBII thyroid binding immunoglobulin

http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=45997
<http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm>



THYROTOXICOSIS

WHAT IS THE STUDY ABOUT?

Hospitalization for arrhythmias and cardiovascular disease may be increased in patients with hyperthyroidism treated with radioiodine.

THE FULL ARTICLE TITLE: “Increased long-term cardiovascular morbidity among patients treated with radioactive iodine for hyperthyroidism” It is in the March 2008 issue of *Clinical Endocrinology (Oxf)* (Volume 68, Issue 3, pages 450-57. The authors are S Metso, A Auvinen, J Salmi, H Huhtala, and P Jaatinen. http://www.ncbi.nlm.nih.gov/pubmed/17941909?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Some long-term studies find an increase in cardiovascular disease (CVD) mortality in patients with hyperthyroidism treated with radioactive iodine (¹³¹I). However, hyperthyroidism itself may account for the increase in CVD mortality.

WHAT WAS THE AIM OF THE STUDY?

The aim of this study was to compare the rate and causes of hospitalization in patients with hyperthyroidism that were treated with ¹³¹I compared with the general population.

WHO WAS STUDIED?

This Finnish population-based case-control study comprised 2611 patients with hyperthyroidism treated with radioiodine (¹³¹I); 16.5% were men and 83.5% were women. Age and gender-matched controls were selected from a population registry.

HOW WAS THE STUDY DONE?

The cause of hospitalization was classified into 13 general groups, which included infectious disease, gastrointestinal disease, and fracture, and CVD was further subclassified as hypertension, coronary artery disease, pulmonary circulation disorders, arrhythmias, heart failure, cerebrovascular diseases, and diseases of other arteries and cerebrovascular diseases. The rates of hospitalization were compared with that in an age-matched group in the general population.

WHAT ARE THE RESULTS OF THIS STUDY?

The median age of study subjects and controls was 62 years (range, 49 to 72) and the median follow-up period was 9.0 years for the patient and control groups. For both groups, CVD was the most frequent cause of hospitalization. Still, the rate

of hospitalization was higher in the patient group as compared with the control group. The risk remained elevated for as long as 35 years after ¹³¹I therapy.

Hospitalization rates for CVD were elevated only among patients treated with 7 to 10 mCi of ¹³¹I, and were about 20% higher than the general population. Patients treated with antithyroid drugs for less than 3 months or for more than 2 years were at increased risk of hospitalization due to CVD as compared with controls. Age at the time of treatment predicted an increased risk of hospitalization compared with controls, and was greatest in patients aged 60 to 98 years.

The clinical factors predicting hospitalization for CVD were toxic multinodular goiter, older age at first ¹³¹I, cumulative ¹³¹I dose, and duration of antithyroid drug therapy. Treatment with ¹³¹I was associated with a 20% increased risk of hospitalization for infectious disease, gastrointestinal disease, and for fracture, which was more common in women 50 years of age or older than in younger women or men.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

In another study, the authors found an increased incidence of cancer in this same group after radioiodine treatment of hyperthyroidism.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

The main limitation of this study is the high likelihood of selection bias. Only hospitalized patients were studied leaving out those who never were hospitalized. Also it is difficult to understand how patients in this cohort treated could have an increased incidence or cancer as the result of receiving very small amounts of ¹³¹I. Moreover it is difficult to reconcile a 35 year adverse effect of a small amount of ¹³¹I. It is much more likely that the findings are due to thyrotoxicosis

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Patients with hyperthyroidism treated with radioiodine may be at increased risk of long-term morbidity and hospitalization for arrhythmias and cardiovascular disease, which it is more likely an effect of hyperthyroidism than radioiodine.

ABBREVIATIONS & DEFINITIONS

CVD is cardiovascular disease.

¹³¹I is radioactive iodine



THYROTOXICOSIS

WHAT IS THE STUDY ABOUT?

Health status, mood and cognition in experimentally induced subclinical thyrotoxicosis.

THE FULL ARTICLE TITLE: “Health status, mood and cognition in experimentally-induced subclinical thyrotoxicosis.” It is in the May 2008 issue of the *Journal of Clinical Endocrinology and Metabolism* (volume 93 Issue 5, pages 1730-36). The authors are MH Samuels, KG Schuff, NE Carlson, P Carello, and JS Janowsky. http://www.ncbi.nlm.nih.gov/pubmed/18285414?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.PubmedResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

The authors recently found that subclinical hypothyroidism leads to decrements in health status, mood, and working memory.

WHAT WAS THE AIM OF THE STUDY?

The aim of this double-blind, randomized, crossover study was to establish whether subclinical thyrotoxicosis also alters health status, mood, and cognitive function.

WHO WAS STUDIED?

In all, 33 adult volunteers with hypothyroidism were studied.

HOW WAS THE STUDY DONE?

Subjects were randomly assigned to receive either their usual doses of levothyroxine (L-T₄) (euthyroid arm) or higher doses of L-T₄ aimed at achieving a low serum TSH mU/L (subclinical thyrotoxicosis arm). Subjects were then tested with SF-36 and POMS (See Box) and Hyperthyroid Symptom Scale for symptoms of thyrotoxicosis. A battery of tests for different forms of memory was administered to assess different cognition areas of the brain.

WHAT WERE THE RESULTS OF THE STUDY?

Study subjects were unable to reliably predict which arm was the subclinical thyrotoxicosis arm. The study found a slight impairment of self-perceived physical health status but found improvements in mental health and mood in subclinically thyrotoxic volunteers. Motor learning was also improved.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

This study model circumvents the limitations in studying endogenous subclinical hyperthyroidism, such as subject recruitment and subjects' awareness of their thyroid status. It also circumvents limitations in studying patients receiving suppressive L-T₄ doses for nodular thyroid disease or thyroid cancer,

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Patients with subclinical thyrotoxicosis experience significant improvements in mood and motor learning but have minor declines in self-perceived general and physical health status. The two studies suggest that different parts of the brain are affected with subclinical hyperthyroidism and hypothyroidism.

ABBREVIATIONS & DEFINITIONS

Pituitary-thyroid feed-back regulation. The pituitary gland behaves like a thermostat and the thyroid gland acts as a furnace while thyroid hormones play a role much like ambient heat.

TSH (thyrotropin) is pituitary **T**hyroid **S**timulating **H**ormone, which stimulates the thyroid gland to release thyroid hormone.

Hypothyroidism occurs when the thyroid fails to make sufficient thyroid hormone and the patient develops gradations of hypothyroidism from overt to subclinical.

Thyroxine (T₄) is the main form of thyroid hormone made by the thyroid gland but much of it is converted in the body to **Triiodothyronine (T₃)** is the most potent form of thyroid hormone.

Hyperthyroidism = overactive thyroid gland.

Thyrotoxicosis A syndrome caused by an excess of thyroid hormone.

Subclinical Hyperthyroidism An asymptomatic condition with a low TSH and normal thyroid hormone levels.

Euthyroid = is normal thyroid function

SF-336 A multipurpose health survey of health and

POMS The Profile of Mood States (below for links to SF-36 and POMS)

<http://www.qualitymetric.com/sf36/spine.pdf>

http://www.imagesoftheself.com/profile_moodStates.pdf



HYPERTHYROIDISM

WHAT IS THE STUDY ABOUT?

More patients with TSH levels <0.05 mIU/L progress to overt hyperthyroidism than those with serum TSH levels ranging from 0.05 to 0.1 mIU/L.

THE FULL ARTICLE TITLE: “The natural history of subclinical hyperthyroidism in patients below the age of 65 years.” It is in the March 2008 issue of *Clinical Endocrinology (Oxf)* (Volume 68 Issue 3, pages 491-92). The author is PW Rosario.

<http://www.ncbi.nlm.nih.gov/pubmed/17803710?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Although it usually does not progress to overt hyperthyroidism, subclinical hyperthyroidism it is more common with very low serum TSH. It has been suggested that the course of subclinical hyperthyroidism is influenced by its cause, with a higher rate of spontaneous cessation in Graves’ disease, but most such studies have been conducted on individuals over 60 years of age.

WHAT WAS THE AIM OF THE STUDY?

This study was aimed at identifying the course of subclinical hyperthyroidism in a patient cohort younger than age 60 years.

WHO WAS STUDIED?

Sixty women younger than 65 years old were enrolled in the study if their serum TSH was <0.1 mIU/L (the level that denotes thyrotoxicosis) and they had no elevations of serum thyroid hormone levels or a history of thyroid disease or other conditions that might interfere with the study.

HOW WAS THE STUDY DONE?

The study subjects underwent a 2-year follow-up period during which they had no therapeutic interventions. Thyrotoxicosis was caused by Graves’ disease in 31% of the study subjects and 50% had toxic multinodular goiter or a single toxic nodule. Patients had serial thyroid function tests during the study period.

WHAT WERE THE RESULTS OF THE STUDY?

Serum TSH spontaneously returned to normal in 20% of the patients with nodular disease and in 13% with Graves’ disease, and TSH improved in 27% with nodular disease and in 20% with Graves’ disease. Subclinical hyperthyroidism persisted in 33.3% with nodular disease and in 27% with Graves’ disease. Among patients with very low serum TSH levels, overt hyperthyroidism developed in 26% with nodular thyroid disease and 50% with Graves’ disease and only 4 patients developed overt hyperthyroidism.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

Earlier studies that have addressed the question of the evolution of subclinical hyperthyroidism involved elderly patients of whom most had subclinical hyperthyroidism associated with multinodular goiter. These studies collectively indicated that a subnormal serum TSH is more likely to persist in patients with goiter or when the initial serum TSH value is <0.1 mIU/L and that only a minority of patients progress to overt hyperthyroidism. This is in contrast to the findings in this study.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

Studies show that patients with subclinical thyroid dysfunction often have thyroid function tests that undergo rapid and dramatic swings over several years when they have not been subject to therapy.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

More patients with TSH levels <0.05 mIU/L progress to overt hyperthyroidism than those with serum TSH levels ranging from 0.05 to 0.1 mIU/L.

Patients younger than 65 years of age who have subclinical hyperthyroidism have a somewhat different outcome than older patients, depending on the cause of the disease. After a 2-year follow-up period without therapeutic intervention, the progression rate to overt hyperthyroidism is about 10% per year for toxic nodular disease and about 20% for Graves’ disease. Serum TSH levels spontaneously return to normal in more patients with toxic nodular disease than in patients with Graves’ disease. These results are very different than those in older patients.

ABBREVIATIONS & DEFINITIONS

TSH Thyroid stimulating hormone (thyrotropin) is a pituitary hormone that stimulates the release of thyroid hormone from the thyroid gland. TSH levels decrease when the thyroid gland produces excess levels of thyroid hormone.

Subclinical Hyperthyroidism An asymptomatic condition in which patients have low TSH levels with normal serum thyroid hormone levels. There are many underlying causes of this condition, such as Graves’ disease, thyroid nodules, and treatment with thyroid hormone (levothyroxine)



THYROID CANCER

WHAT IS THE STUDY ABOUT?

Patients with large follicular thyroid cancers often develop T_3 toxicosis. However, T_3 is not commonly measured in patients with thyroid cancer.

THE FULL ARTICLE TITLE: “3,5,3’-Triiodothyronine thyrotoxicosis due to increased conversion of administered levothyroxine in patients with massive metastatic follicular thyroid carcinoma.” It is in the June 2008 issue of the *Journal of Clinical Endocrinology and Metabolism* (Volume 93 Issue 6, pages 2239-42). The authors are A Miyauchi, Y Takamura, Y Ito, A Miya, K Kobayashi, F Matsuzuka, N Amino, N Toyoda, E Nomura, and M Nishikawa, M. http://www.ncbi.nlm.nih.gov/pubmed/18397985?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Patients with widely metastatic thyroid cancer may have triiodothyronine (T_3) thyrotoxicosis due to increased D-1 and D-2 activity that converts thyroxine (T_4) to T_3 in amounts sufficient to cause thyrotoxicosis, but the prevalence, diagnosis, and treatment of this problem have not been fully elucidated.

WHAT WAS THE AIM OF THE STUDY?

This study was aimed at identifying the prevalence and cause of T_3 toxicosis in patients with thyroid cancer and the diagnostic clues for the diagnosis.

WHO WAS STUDIED?

The study subjects were 58 patients with metastatic thyroid cancer measuring 2 cm or larger in diameter; 54% had papillary cancer, 35% had follicular cancer, and 12% had medullary thyroid cancer. Study controls were 17 patients with papillary thyroid cancer who had no sign of tumor recurrence after total thyroidectomy.

HOW WAS THE STUDY DONE?

Frozen stored sera remaining from past measurements were used to measure FT_3 to clarify the course of change in these patients. Three stored frozen tumors, two primary tumors and one metastatic subcutaneous tumor from two patients were studied for measurement of D-1 and D-3 activity.

WHAT WERE THE RESULTS OF THE STUDY?

In all, 20% of 20 patients had T_3 thyrotoxicosis; their mean age was 59.5 years. There were no statistical differences in the mean age, in levels of TSH and FT_4 . Analyses of stored sera from two patients with T_3 thyrotoxicosis revealed that FT_3 levels had started to increase about 2 to 4 years earlier while FT_4 levels gradually declined but remained in the normal range. Also, in one patient

both FT_4 and FT_3 declined to undetectable levels during a 1-month period in which L- T_4 was stopped to facilitate ^{131}I therapy.

Withdrawal of L- T_4 in the four patients with thyrotoxicosis for 1 week resulted in a decrease of serum FT_4 and FT_3 levels in all four patients, indicating that the high T_3 levels were not produced by functioning metastases but instead originated from increased conversion of T_4 to T_3 in tumor tissue. This was documented by measurement of D-1 and D-2 in tumor specimens that revealed high levels of these enzymes.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

In 2003 Kim et al. first identified three patients with large or widely metastatic follicular thyroid cancer who had persistently increased T_3/T_4 ratios in the absence of T_3 production by the tumor. They assayed D-1 and D-2 activity in a large follicular thyroid cancer resected from one of these patients and found that D-2 was 8-fold higher than in normal human thyroid tissue and resection of the tumor, leaving the left thyroid lobe intact, normalized the serum T_3/T_4 ratio. They concluded that this had probably come about by the increase in D-2 activity

WHAT ARE THE LIMITATIONS OF THIS STUDY?

There are no potential limitations in this study.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

One in five patients with widely metastatic follicular thyroid cancer has T_3 thyrotoxicosis from increased tumor deiodinase activity that can be identified by measuring serum T_3 levels and stopping levothyroxine therapy.

ABBREVIATIONS & DEFINITIONS

T_4 is levothyroxine, a molecule that contains 4 iodine atoms.

T_3 is triiodothyronine, a molecule that contains 3 iodine atoms.

FT_4 is free thyroxine (a type of circulating thyroid hormone).

FT_3 is free triiodothyronine (another type of circulating thyroid hormone)

Conversion of T_4 to T_3 The thyroid gland secretes considerably more T_4 than T_3 which is biologically much more potent than T_4 .

Deiodinases Enzymes that convert T_4 to T_3 . Iodothyronine D-1 is mainly expressed in the liver, kidney, and thyroid gland and D-2, is mainly expressed in the brain, pituitary, cardiac and skeletal muscle, and placenta convert T_4 to T_3 .

TSH is thyrotropin, thyroid stimulating hormone



HYPOTHYROIDISM

WHAT IS THE STUDY ABOUT?

Does levothyroxine (L-T₄) therapy restore serum T₃ levels in patients with hypothyroidism?

THE FULL ARTICLE TITLE: “Triiodothyronine levels in athyreotic individuals during levothyroxine therapy.” It is in the February 2008 issue of the *Journal of the American Medical Association* (Volume 299, Issue 7, pages 769-777). The authors are J Jonklaas, B Davidson, S Bhagat, and SJ Soldin, The abstract can be obtained from: <http://www.ncbi.nlm.nih.gov/pubmed/18285588?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Clinical trials have demonstrated that adding liothyronine (T₃) to levothyroxine (L-T₄) confers no consistent benefit to patients being treated for hypothyroidism. However, there is no direct evidence that T₃ deficiency is avoided by using L-T₄ alone. As 80% of circulating serum T₃ is derived from the peripheral conversion of L-T₄ to T₃, thyroidectomy theoretically deprives the individual of the 20% contribution of direct T₃ secretion from the thyroid.

WHAT WAS THE AIM OF THE STUDY?

The study is designed to compare preoperative serum T₃ levels in patients with normally functioning thyroid glands with the T₃ levels in the same patients after their thyroid was surgically removed and were being treated with L-T₄ alone.

WHO WAS STUDIED?

The study subjects were 50 patients with normal thyroid function (euthyroid) aged 18 to 65 years who were scheduled for total thyroidectomy for suspected or known thyroid cancer, goiter, or benign nodular thyroid disease.

HOW WAS THE STUDY DONE?

Thyroid hormone levels were measured before thyroidectomy in individuals not receiving thyroid hormone therapy, and again after surgery when they were being treated with L-T₄ alone. Postoperatively, patients with benign thyroid disease were given L-T₄ (1.7 µg/kg daily) replacement therapy aimed at keeping the serum TSH levels in the normal range, and others were given L-T₄ (2.2 µg/kg daily) to maintain the serum TSH level below normal for the treatment of thyroid cancer. The L-T₄ doses were adjusted during the two postoperative (third and fourth) thyroid profiles to achieve the treatment goals. Patients underwent a complete history and physical examination and had two separate thyroid profiles before and two after thyroidectomy when they were taking L-T₄ and had achieved stable serum thyrotropin (TSH) levels. At the end of the study, the medication history and physical examination were repeated.

WHAT WERE THE RESULTS OF THE STUDY?

By the end of the study, there were no significant decreases in serum T₃ levels in patients receiving L-T₄ therapy as compared with their prethyroidectomy T₃ levels.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

This is the first study to assess serum T₃ levels in patients taking L-T₄. Other studies published to date compare patients with hypothyroidism already taking L-T₄ who were either continued on L-T₄ therapy or switched to T₄/T₃ combination therapy.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

One potential limitation is that the patients with benign thyroid disease had varying amounts of remnant thyroid tissue. It is unlikely that this accounted for the results.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This unique study provides clear evidence that adding liothyronine (T₃) to levothyroxine replacement therapy is not necessary to achieve normal serum T₃ levels and euthyroidism.

ABBREVIATIONS & DEFINITIONS

TSH is thyroid stimulating hormone (thyrotropin)

T₄ is levothyroxine, a molecule that contains 4 iodine atoms. This is the main hormone secreted by the thyroid gland and the main hormone used for replacement therapy in patients with hypothyroidism.

T₃ is triiodothyronine, a molecule that contains 3 iodine atoms and is the most potent form of thyroid hormone. Liothyronine (Cytomel) is a potent short acting form of T₃ that is not ordinarily used for replacement therapy.

This is the most potent form of thyroid hormone that is mainly derived from enzymes that remove one iodine atom from T₄

Conversion of T₄ to T₃ The thyroid gland secretes considerably more T₄ than T₃ which is biologically much more potent than T₄. Deiodinases The conversion of T₄ to T₃ is made by several enzymes (deiodinases) expressed in the liver, kidney, thyroid gland and other tissues which provide 80% of circulating serum T₃ levels.



HYPOTHYROIDISM

WHAT IS THE STUDY ABOUT?

The diagnosis and management of subclinical hypothyroidism

THE FULL ARTICLE TITLE: “Interval between tests and T₄ estimation method influence outcome of monitoring of subclinical hypothyroidism..” It is in the May 2008 issue of *Thyroid* Volume 93 Issue 5, pages 1634-40). The authors are J Karmisholt, S Andersen, and P Laurberg. http://www.ncbi.nlm.nih.gov/pubmed/18303081?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Although subclinical hypothyroidism is a common diagnosis, there is no consensus concerning when treatment should be initiated and how untreated patients should be monitored.

WHAT WAS THE AIM OF THE STUDY?

This prospective study evaluates the diagnostic reliability of the information obtained from sequential clinical observations and monthly thyroid-function tests measured over a 13 month period.

WHO WAS STUDIED?

The study subjects were selected from 34 individuals of mean age 57 years who had serum TSH levels of 5 to 12 μ IU/ml (above normal) and thyroxine (T₄) and triiodothyronine (T₃) within the normal range all of which remained stable on repeated testing over 3 months.

HOW WAS THE STUDY DONE?

At each visit, serum T₄ was measured by three different methods, and signs and symptoms of hypothyroidism were evaluated. The study participants were evaluated monthly for 13 months. Blood samples were obtained and thyroid function tests were determined immediately, and at the end of the study in frozen serum samples stored at -20° C.

WHAT WERE THE RESULTS OF THE STUDY?

During the 13-month study period, the criteria for subclinical hypothyroidism were satisfied in 15% to 100% of the patients at various times, and in 29% of the patients during all the visits; the diagnoses were variable 67% of the time. Overall, the hypothyroid score did not differ between patients with overt or subclinical hypothyroidism. Using these observations, subclinical hypothyroidism would have been diagnosed during 74% of the visits, overt hypothyroidism in 22%, and euthyroidism in 4%. The diagnoses also varied according to the three different estimates of T₄.

Using thyroid-function tests performed every 2nd, 3rd, 4th, 6th or 12th month, resulted in a steady fall in the diagnosis

of overt hypothyroidism and a rise in the diagnosis of subclinical hypothyroidism.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

A scientific review concluded that data relating a serum TSH level higher than 10 μ IU/ml to elevations in serum cholesterol were rated as fair but data relating to benefits of levothyroxine treatment were rated as insufficient. All other associations of symptoms and benefit of treatment were rated as insufficient or absent.

The clinical review concluded that: “Because of the substantial uncertainty concerning the consequences of untreated subclinical hypothyroidism and hyperthyroidism, as well as the benefit of initiating treatment, patient preferences are important in deciding on management of subclinical disease.”

See the web links below that explore the information about this subject:

http://www.ncbi.nlm.nih.gov/pubmed/14722151?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

http://www.ncbi.nlm.nih.gov/pubmed/14722150?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

WHAT ARE THE LIMITATIONS OF THIS STUDY?

This unique study should be verified in another group of patients

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The diagnosis of subclinical hypothyroidism is severely limited by a single set of thyroid function tests and the biologic variation in thyroid testing from visit to visit. Treatment with levothyroxine should be withheld until the diagnosis is verified, but even then it may not be required unless there are extenuation circumstances, particularly patient preference.

ABBREVIATIONS & DEFINITIONS

TSH Thyroid stimulating hormone (thyrotropin) is a pituitary hormone that stimulates the release of thyroid hormone from the thyroid gland. TSH levels decrease when the thyroid gland produces excess levels of thyroid hormone.

T₄ is thyroxine (the most common circulating thyroid hormone)

Subclinical Hypothyroidism An asymptomatic condition in which patients have higher than normal TSH levels with normal serum thyroid hormone levels. A common cause of this is autoimmune thyroiditis (Hashimoto’s disease, especially in women)



THYROID HORMONE THERAPY

WHAT IS THE STUDY ABOUT?

Intestinal absorption of thyroid hormone may be impaired by drugs that impair gastric acid secretion.

THE FULL ARTICLE TITLE: “The effect of famotidine, esomeprazole, and ezetimibe on levothyroxine absorption.” It is in the May 2008 issue of *Thyroid* (volume 18 Issue 5, pages 493-8). The authors are S Ananthakrishnan, LE Braverman, R Levin B Magnani, and EN Pearce.

<http://www.ncbi.nlm.nih.gov/pubmed/18466075?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Gastric acid suppression is inconsistently reported to interfere with levothyroxine (L-T₄) absorption.

WHAT WAS THE AIM OF THE STUDY?

This is a prospective study of the absorption of L-T₄ in normal volunteers taking famotidine (Pepcid, a histamine H-2 antagonist) esomeprazole, (Nexium a proton-pump inhibitor) and ezetimibe (Zetia, a lipid-lowering drug that inhibits intestinal absorption of cholesterol).

WHO WAS STUDIED?

The study subjects were 30 carefully screened healthy, euthyroid volunteers.

HOW WAS THE STUDY DONE?

Volunteers were assigned to one of three independent study groups, famotidine, esomeprazole, and ezetimibe, with 10 in each group. The mean age was 28.1, 26.1 and 27 years, respectively, in each group. L-T₄ absorption was tested before study, and the final L-T₄ absorption test was performed approximately 1 week after the subjects were assigned to drug administration and immediately before a third and final L-T₄ absorption test.

The study was performed as follows in the three study groups: 1 week of 20 mg famotidine (Pepcid) twice daily with meals, or 1 week of 40 mg esomeprazole (Nexium) daily with breakfast, or a single 10-mg dose of ezetimibe (Zetia). A 1-week administration of the gastric acid suppressive medications was selected to achieve a gastric pH >4 (range, 12-19).

Patients were divided into three normal reference groups that were selected with increasingly more stringent criteria to identify those without evidence of thyroid disease. TSH was retested by both older and contemporary laboratory methods.

WHAT WERE THE RESULTS OF THE STUDY?

Mean peak serum thyroxine levels did not change significantly before and after famotidine, esomeprazole, or ezetimibe. Serum fasting gastrin levels were significantly higher than baseline levels as a result of taking the each of the drugs that impair gastric acid secretion.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

The rate of thyroid hormone absorption can be estimated by the ingestion of radioactive iodine-labeled L-T₄ or simply with large oral doses of L-T₄, in the range of 600 µg. These observations have led to the discovery of a number of conditions that can lead to malabsorption of L-T₄, ranging from intestinal disease, timing of L-T₄ ingestion with meals, and the simultaneous use of drugs that inhibit L-T₄ absorption such as iron and calcium. Previous studies have shown that patients with impaired gastric acid secretion require an increased dose of L-T₄, suggesting that normal gastric acid secretion is necessary for effective absorption of oral L-T₄.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

The main limitation is that this was an acute study and the two gastric acid inhibitors are likely to cause some malabsorption when L-T₄ is taken over an extended period, or when patients taking these drugs have gastritis.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that normal subjects taking famotidine and esomeprazole for a short period of time does not impair thyroid hormone absorption. However, taking these drugs for an extended time would likely cause L-T₄ malabsorption.

ABBREVIATIONS & DEFINITIONS

L-T₄ is levothyroxine, the standard drug for treatment of hypothyroidism and thyroid cancer

Gastrin is a stomach hormone that stimulates stomach acid secretion

Famotidine (Pepcid), a histamine H-2 antagonist that inhibits gastric acid secretion

Esomeprazole, (Nexium a proton-pump inhibitor) that lowers gastric acid secretion

Ezetimibe (Zetia) a lipid-lowering drug



THYROID HORMONE THERAPY

WHAT IS THE STUDY ABOUT?

Coffee interferes with the intestinal absorption of levothyroxine.

THE FULL ARTICLE TITLE: “Altered Intestinal Absorption of L-Thyroxine Caused by Coffee.” It is in the March 2008 issue of *Thyroid* (volume 18 Issue 3, pages 293-301). The authors are S Benvenega, L Bartolone, MA Pappalardo, A Russo, D Lapa, G Giorgianni, G Saraceno, G., and F Trimarchi. http://www.ncbi.nlm.nih.gov/pubmed/18341376?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed.ResultsPanel.Pubmed_RVDocSum

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Many things interfere with gastrointestinal absorption of L-T₄ (See Box) The authors of this study have previously reported cases of delayed intestinal absorption of L-T₄ and have thus been more than usually attentive to this problem, eliciting detailed histories from their patients about the use of other drugs and the dietary habits patients follow when taking L-T₄.

WHAT WAS THE AIM OF THE STUDY?

The authors found that several patients were consistently drinking coffee or espresso to facilitate swallowing L-T₄ pills or were taking L-T₄ with water followed shortly by drinking coffee or espresso, suggesting that this might be the cause of the problem. The study was designed to test gastrointestinal absorption of L-T₄ in patients taking L-T₄ while simultaneously drinking coffee or espresso.

WHO WAS STUDIED?

The study subjects were eight patients, all of whom were women. Their mean age was 45 years and their serum TSH levels were 2.7 μIU/ml (normal range, 2.9 to 55). Ten healthy volunteers, four men and six women aged 24 to 52 years, were also studied as controls.

HOW WAS THE STUDY DONE?

L-T₄ absorption was tested in patients divided into several groups, some taking L-T₄ with water alone, others using espresso alone to help swallow their L-T₄ pills, and in other cases volunteers used water alone with L-T₄ and espresso 1 hour later, and lastly L-T₄ was taken with bran in water.

WHAT WERE THE RESULTS OF THE STUDY?

The effect of espresso on L-T₄ absorption was variable, and was present only if espresso was swallowed simultaneously with the L-T₄, but not 60 minutes later. Taking L-T₄ with espresso lowered the average and peak incremental rise of serum T₄ by a minimum of 25% in one patient, to a maximum of 57% in

patient in another patient. Reduction in the maximal incremental rise in serum levels ranged from 14% in one patient to 49% in another, while overall reduction ranged from 23% to 55%. Compared to water, espresso delayed the peak serum increase in serum T₄ from 0 in one patient to 90 minutes in another. The study clearly showed that drinking espresso or coffee may interfere with intestinal absorption of L-T₄ if one drinks it with or shortly after levothyroxine is taken. This pattern of taking espresso or coffee with L-T₄ was highly consistent among the eight study patients. The effect was significant, but is not as severe as that produced by Maalox or by bran ingested at the time L-T₄ is taken.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

Approximately 62% to 82% of the oral dose of levothyroxine is absorbed by the upper intestine. The rate of absorption can be estimated by simply giving large oral doses of thyroid hormone. This has led to the discovery of a number of conditions that can lead to malabsorption of thyroid hormone.

WHAT ARE THE LIMITATIONS OF THIS STUDY?

Coffee does not change the gastric pH, nor does it impair gastric emptying and intestinal transit in normal volunteers. Because the study is retrospective, it relied on the recollections of patients rather than a systematic recording of the timing of meals and coffee ingestion.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The observations are robust enough, and the recommendations simple enough to warn patients about this problem and to add coffee to the list of things to be avoided at the same time that L-T₄ is taken.

ABBREVIATIONS & DEFINITIONS

L-T₄ is levothyroxine, the standard drug for treatment of hypothyroidism and thyroid cancer

Gastrointestinal malabsorption of thyroid hormone

Many things interfere with levothyroxine (L-T₄) absorption, such as iron, bile acid-binding resins, cholestyramine and colestipol, over-the-counter drugs containing iron and calcium, gastric conditions such as achlorhydria, and food ingestion around the time L-T₄ is taken. Many other drugs and conditions impair absorption of L-T₄.



THYROID AND ERECTILE DYSFUNCTION

WHAT IS THE STUDY ABOUT?

Men with hyperthyroidism or hypothyroidism commonly have erectile dysfunction .

THE FULL ARTICLE TITLE: “Erectile dysfunction in patients with hyper- and hypothyroidism: how common and should we treat? ” It is in the May 2008 Issue of the *Journal of Clinical Endocrinology and Metabolism* (Volume 93 Issue 5, pages 1815-1819). The authors are GE Krassas, K Tziomalos, F Papadopoulou, N Pontikides, and P Perros. The abstract can be obtained from: <http://www.ncbi.nlm.nih.gov/pubmed/18270255?dopt=Citation>

WHAT IS KNOWN ABOUT THE PROBLEM BEING STUDIED?

Erectile dysfunction (ED) is a common disability associated with aging and numerous diseases. Symptoms of ED for 3 months are usually required to establish the diagnosis.

WHAT WAS THE AIM OF THE STUDY?

The aim was to investigate the impact of hyperthyroidism and hypothyroidism on the health of male sexual function and dysfunction.

WHO WAS STUDIED?

The study included 71 subjects, 27 with hyperthyroidism and 44 with hypothyroidism, and 71 euthyroid controls. The mean age was 52.6 years for the hyperthyroid group, 55.9 for the hypothyroid group, and 54 for the control group.

HOW WAS THE STUDY DONE?

The study was done with the Sexual Health Inventory for Males (SHIM) instrument, which is a validated and widely used five-item questionnaire concerning a man's ability to attain and maintain an erection.

WHAT WERE THE RESULTS OF THE STUDY?

In all, 79% of men with thyroid dysfunction had a SHIM score ≤ 21 , indicating some degree of ED, 52% with hypothyroidism and 27% with hyperthyroidism, compared with 24 controls (34%) with a similar ED score. Severe ED (SHIM ≤ 10) was found in almost 38%, (295%) with hypothyroidism and 29.6% with hyperthyroidism, as compared with 25 % in 6 controls. ED was found in a significantly larger number of patients with hyperthyroidism (71%) and hypothyroidism (85%) as compared with controls (25%).

As assessed by the international SHIM instrument, approximately 80% of the patients in this study had ED, as

compared with 37.5% of the Back to Table of Contents controls. After euthyroidism was restored, 30% of the patients had ED, a rate similar to that in controls.

HOW DOES THIS COMPARE WITH OTHER STUDIES?

and similar tests have been widely used since medications to treat ED became available. A 2008 review by Derogatis points out that the recent recognition of the high prevalence of sexual dysfunctions and disorders in our society, along with the development of drugs to treat ED, has resulted in a significant expansion in the development of valid and reliable measures of sexual function/dysfunction. He explains that the instruments generally are brief self-report inventories, typically requiring 10 to 20 minutes of patient time for completion. All of these instruments, which must adhere to recently prescribed rigorous guidelines set forth by the Food and Drug Administration, have been demonstrated to be valid and reliable indicators of the status and quality of sexual functioning in both men and women. The review by DeRogatis is available at <http://www.ncbi.nlm.nih.gov/pubmed/17703221?dopt=Citation>

WHAT ARE THE LIMITATIONS OF THIS STUDY?

The mechanism by which thyroid dysfunction can cause ED has not been investigated.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Men with thyroid dysfunction commonly have ED that is reversible with restoration of the euthyroid state. Although screening for ED is recommended for these men, specific treatment should be postponed for at least 6 months after restoring euthyroidism because it may take this long for ED to spontaneously resolve.

ABBREVIATIONS & DEFINITIONS

ED is erectile dysfunction

SHIM Sexual Health Inventory for Males is a validated and widely used five-item questionnaire concerning a man's ability to attain and maintain an erection.

SHIM Score Mild ED 17 to 21, Moderate ED, 1–16, Severe ED ≤ 10

The following web link has a summary of the test questions:

http://www.erectilefunction.org/tool_kit/Shim.pdf