**Topic:** ENDOCRINE FUNCTION AFTER RADIOIODINE THERAPY

**Title:** Testicular function after radioiodine therapy in patients with thyroid cancer.

**Authors:** Rosario PD, Barroso AL, Rezende LL, et al. (Belo Horizonte, Brasil)

**Reference:** Thyroid 16: 667-670, 2006

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**SUMMARY**

**Background:** The aim of the study was to assess testicular function in patients treated with high-dose radioiodine.

**Patients and methods:** Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels were determined in 52 men with thyroid carcinoma before and 6, 12 and 18 months after RI therapy (3.7-5.5 GBq I^{131}; mean of 4.5 GBq I^{131}) (Group 1) and were also determined before and 18 months after the last RI therapy in 22 patients who received high cumulative activities (13-27.7 GBq I^{131}, mean of 20.3 GBq I^{131}) (Group 2).

**Results:** FSH levels were increased 6 months after therapy in all patients of group 1, while a decline was observed after 12 months, with 37 of 52 (71%) patients presenting normal FSH levels at this time. FSH values returned to normal in all patients after 18 months. In group 2, 12 of 22 (55%) patients presented elevated FSH and 8 (66%) of these individuals had oligospermia. Six months after RI therapy, increased LH levels were observed in only 5 of 52 (10%) patients of group 1, which returned to normal after 12 months, and in 5 of 22 (22%) of group 2. All patients showed normal testosterone levels.

**Conclusions:** RI therapy may cause impairment of testicular function. A generally transient increase in FSH is highly common but is usually reversed within 18 months. Oligospermia was common (one third) after high cumulative RI activities. Because the authors did not perform a spermiogram before RI therapy, they cannot state that high cumulative I^{131} activities cause permanent infertility. They recommend the routine use of sperm banks in the case of men who still wish to have children and who must undergo therapy with I^{131} activities of 14 GBq or more or in the case of patients with pelvic metastases.

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**COMMENT**

Side effects are frequent after large activities of radioiodine (R-I^{131}), given for the ablation of thyroid remnants or metastases in patients with thyroid cancer. The frequency of infertility secondary to radiation has probably been underestimated in young males and studies on testicular function after R-I^{131} are scarce, although endocrine testicular function seems to be less sensitive to the effects of radiation. The present findings confirm these notions, in which no decrease in free testosterone was observed, even in the group of patients receiving a high cumulative R-I^{131} activity. However, the changes seen for FSH and LH suggest a possible and transient compensated Leydig cell insufficiency. The high rate of oligospermia (despite the methodological weaknesses of the study) observed in the males receiving high radioactive doses of R-I^{131} led the authors to propose to use...
sperm banks before high R-1\(^{131}\) activities are administered in young males with thyroid cancer.  
(Daniel Glinoer, M.D.; Ph.D.)

See Figure below

FIG. 2. Testicular function of patients who received a high \(^{131}\)I activity (≥ 13 GBq).
CASE REPORT

A 46 year old man was referred to the endocrine clinic of the City Hospital (Birmingham, UK) in July 2003 with a history of weight loss, sweating and diarrhoea. On examination, he presented clear signs of severe thyrotoxicosis, rapidly confirmed by laboratory tests (free T4: 93 pM/L; free T3: 30 pM/L; undetectable serum TSH). He was treated successfully with carbimazole during a 1 year period. He then presented a recurrence of hyperthyroidism at the end of therapy and was given carbimazole again. Once he became euthyroid, radioiodine (RI-131) treatment was planned in view of recurrent hyperthyroidism. December 2004 he was given 400 MBq of RI-131 (~ 11 milliCi). The nuclear medicine department gave him a the radionuclide instruction card highlighting the usual precautions to be taken. However, the card did not mention the risk of radiation detectors to be triggered. Six weeks later, he went to the USA for a holiday. At Orlando airport he set off the security alarm at check-in. He was immediately detained and strip-searched. Sniffer dogs were also called in. A prolonged period of interrogation ensued. Luckily, the patient was carrying the radionuclide card with him. He was finally released after a long delay and much embarrassment. While narrating this story in the clinic after his return, the patient stated that he would not have made the US journey if he had had any inkling of the harassment he was likely to face.

COMMENT

Given the current political climate, airport authorities are keen to detect any radioactive material being carried aboard airplanes and it is therefore not surprising that anybody setting off radioactive alarms will be subjected to extensive search and questioning. The authors of this short article carried out a literature search and found only four similar case reports: 2 patients arrested, trying to enter the White House for a public visit (1986); a bank vault alarm triggered by a patient who had undergone a Thallium stress test (1988); a radiation alarm set off by radioiodine (25 days after receiving a dose of 4 milliCi of RI-131 for a toxic multinodular goiter) at the airport in Vienna (2004); and finally, two days after undergoing a Thallium-201 myocardial perfusion scan, a pilot triggered a radiation alarm while travelling to Moscow (2004).

Since the case of their patient, the nuclear medicine department in Birmingham has added the following statement on the radionuclide instruction card given to the patients: “airport alarms may be triggered for up to 12 weeks after receiving your therapy dose”. This obviously rare and unfortunate side event after RI-131 therapy is a good lesson for all of us.

(Daniel Glinoer, M.D.; Ph.D.)
Number of days up to which patients might trigger radiation alarms after receiving radioisotopes

<table>
<thead>
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<th>Radionuclide</th>
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<td>Fluoride-18</td>
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<td>Iodine-131</td>
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</table>
**Topic:** “SCH” and “CHD”

**Title:** Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis.

**Authors:** Rodondi N, Aujesky D, Vittinghoff E, et al. (San Francisco, USA and Lausanne, Switzerland)

**Reference:** American Journal of Medicine 119: 541-551, 2006

### SUMMARY

**Purpose:** Subclinical hypothyroidism (SCH) has been associated with elevated cholesterol and increased risk for atherosclerosis, but data on the risk of coronary heart disease (CHD) are conflicting. The authors performed a systematic review to determine whether SCH is associated with CHD in adults.

**Methods:** They searched MEDLINE from 1966 to April 2005, and the bibliographies of key articles to identify studies that provided risk estimates for CHD or cardiovascular mortality associated with SCH. Two authors reviewed independently each potential study for eligibility, assessed methodologic quality, and extracted the data.

**Results:** The authors identified 14 observational studies that met eligibility criteria. SCH increased the risk of CHD (O.R.: 1.65; 95% C.I.: 1.28-2.12). The summary odds ratio for CHD was 1.81 (95% C.I.: 1.38-2.39) in 9 studies adjusted or matched for demographic characteristics, and 2.38 (95% C.I.: 1.53-3.69) after pooling the studies that adjusted for most cardiovascular risk factors. Sensitivity analyses including only population-based studies and those with formal outcome adjudication procedures yielded similar results. Subgroup analyses by type of study design showed a similar trend, but lower risk, in the 5 prospective cohort studies (O.R.: 1.72; 95% C.I.: 1.25-2.38).

**Conclusion:** The present systematic review indicates that subclinical hypothyroidism is associated with an increased risk of CHD. Clinical trials are needed to assess whether thyroxine replacement reduces the risk of CHD in subjects with subclinical hypothyroidism.

### COMMENT

Subclinical hypothyroidism (SCH) refers to subjects who have a slightly elevated serum TSH (4-10 mU/L) and a normal free T4 level. The prevalence of SCH is estimated to represent 3-5% in the population and is correlated to both gender (females > males) and age (old > young). The main cause of SCH is chronic autoimmune thyroiditis, often leading to a progressive atrophy of the thyroid gland and, in turn, variable degrees of hypothyroidism. Already 40 years ago, Bastenie and coll. identified the risk of coronary vascular disease associated with thyroid dysfunction (Lancet, 1967). More recently and despite some conflicting results, many studies have found that subjects with SCH have higher total and LDL cholesterol levels compared with euthyroid subjects. Data on the risk of CHD in subjects with SCH are conflicting, but several considerations should be taken into account to interpret the results of such studies: studies with low power because of
small numbers of CHD events examined; many studies are cross-sectional or case-controlled; etc. In present work, 753 reports were initially identified, of which 719 were excluded because they were unrelated directly to the question asked: is there an association between CHD and thyroid disease? Of the remaining 34 articles selected for more detailed evaluation, 9 studies did not assess the risk of CHD, 5 studies did not provide a specific definition of SCH, 2 studies did not provide risk estimates and C.I., 2 studies did not comprise a euthyroid control group, and 1 study had an incorrect statistical analysis. Finally, only 14 observational studies met the eligibility criteria. On the basis of the present carefully conducted meta-analysis, the authors confirm that SCH is significantly associated with an increased risk of CHD.

Although it cannot be ruled out that biases in the original studies or publication biases might have been present, this study is based on the best currently available data and was carried out according to commonly accepted methodological recommendations to limit the problems encountered with meta-analyses of observational studies. If the present results are confirmed in prospective studies including a large number of CHD-related events, two questions would then become predominant: 1) should populations be systematically screened for the risk of SCH (thyroid antibodies & serum TSH determinations) and SCH patients treated with l-thyroxine; 2) clinical trials should assess whether l-thyroxine replacement therapy reduces the risk of CHD in patients with subclinical hypothyroidism. (Daniel Glinoer, M.D.; Ph.D.)

See Figure below

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**Figure 1** Forest plot of odds ratios (ORs) of coronary heart disease (CHD) associated with subclinical hypothyroidism. ORs (diamonds) and 95% confidence intervals (CIs) (horizontal lines) of the effect of subclinical hypothyroidism on the risk of CHD. CC = case-control study; CS = cross-sectional study; PC = prospective cohort study.
**Topic:** TREATMENT OF HYPOTHYROIDISM

**Title:** Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials.

**Authors:** Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L (Petah-Tiqva & Tel-Aviv, Israël)

**Reference:** Journal of Clinical Endocrinology & Metabolism 91: 2592-2599, 2006

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**SUMMARY**

**Context:** In some patients symptoms of hypothyroidism persist despite therapy with T₄.

**Objectives:** The objective of the study was to compare the effectiveness of T₃-T₄ combination versus T₄ monotherapy for the treatment of clinical hypothyroidism in adults.

**Data sources:** Pubmed, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched in September 2005. References of all included trials were scanned for additional studies. There was no restriction on language, year of publication, or publication status.

**Study selection:** All randomized trials that compared the effectiveness of T₃-T₄ combination versus T₄ monotherapy for the treatment of clinical hypothyroidism in adults were included.

**Data extraction:** The data were extracted by two independent reviewers.

**Data synthesis:** The authors included 11 studies, in which a total of 1216 patients was included. No difference was found in the effectiveness of the combination treatment versus monotherapy in any of the following symptoms: bodily pain, depression, anxiety, fatigue, quality of life, body weight, total serum cholesterol, triglyceride levels, low-density lipoprotein, and high-density lipoprotein. Adverse events did not differ between regimens.

**Conclusions:** T₄ monotherapy should remain the treatment of choice for clinical hypothyroidism.

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**COMMENT**

The routine use of computerized “search engines” and availability of computerized tools for comparing therapeutic trials constitutes one of the bases of evidence-based medicine and, in this approach, meta-analyses have become a mainstay in medical clinical research. At almost every international thyroid congress, we hear new data on hypothyroid patients who don’t feel well under “adequate” T₄ treatment and also new results on the potential advantage of combining T₃ with T₄ for this long term treatment.

Thyroxine is the logical treatment of hypothyroidism for the following main reasons: 1) physiologically, the thyroid gland produces essentially T₄ (and little T₃); 2) T₄ has a long half life (~1 week), hence providing stable quantities of T₃ by peripheral – intracellular – regulation of T₃.
production through the progressive deiodination of T4; 3) there is a log-
decimal inverse correlation between serum TSH and free T4 levels (that does not exist
with free T3); and finally 4) the administration of T3 induces peaks of high
serum T3 levels in the hours following its administration and, therefore, steady-state
levels cannot be achieved with this hormone when given once a day.

The authors undertook a systematic search of potentially relevant publications (N =
503). Of this large database, 490 publications were excluded because they
were not randomized controlled trials (RCT). Of the 13 publications retrieved for
further detailed evaluation, 2 others were excluded (1 because of insufficient data
and 1 because of ‘double’ publication).

Finally, they were left with 11 RCT that
met the eligibility criteria for meta-
analysis, corresponding to a total of over
1,000 patients. These studies are relatively
recent, published from 1999 (Bunevicius)
until 2005 (Appelhof; Escobar-Morreale;
Rodriguez; Saravanan). The main result of
the present analysis was that T3-T4
combination therapy used as replacement
therapy for patients treated for
hypothyroidism provided no advantage
when compared with the standard
monotherapy using T4. There was no
benefit in terms of symptoms (fatigue,
bodily pain, anxiety, depression) and no
improvement in the quality of life. Moreover, the combination therapy led to
no improvement in cognitive efficiency or
the ability to undertake novel tasks,
memory, attention, etc. Finally, lipid
profile was not improved in patients
prescribed the combination treatment. It
should also be mentioned that the trials
varied in the doses of T3 given as well as
duration of treatment. However and despite
these differences, the primary outcomes
did not depend on T3 dose or duration of
prescription. My only personal addition to
this excellent study is that with the only
commercial T3-T4 combination therapy
available in our country, we are often
referred patients who present cardiac or
arrhythmic detrimental side effects
associated with high serum T3 levels.
Monotherapy with appropriate (and
correctly monitored) doses of T4 should
remain the standard treatment for
hypothyroidism.

(Daniel Glinoer, M.D.; Ph.D.)
SUMMARY

Objective: To evaluate if a thyroid nodule with shape taller than wide (antero-posterior/transverse diameter ‘A/T’ > 1) is a good predictor of malignancy independent of the size.

Methods: The authors retrospectively examined the cytological and histological results of 7,455 nodules (5,198 patients) referred for ultrasound-guided fine needle aspiration cytology (US-FNAC) between January 1991 and September 2004.

Results: A suitable FNAC was obtained from 6,135 nodules (4,495 patients): 34.6% were less than 1 cm in diameter (small nodules, SN). A diagnosis of carcinoma was histologically confirmed in 284/349 suspicious lesions after FNAC. The size of carcinoma was not significantly associated with the occurrence of extracapsular growth (large nodules, LN): 10.5% in LN versus 4.9% in SN (non significant) and lymph node metastasis: 23.6% in LN versus 25.0% in SN (non significant). Malignant lesions showed microcalcifications more frequently than benign nodules: 72.2% versus 28.7% (P<0.001 and Odds Ratio = 9.9, with 95% C.I.: 7.2-13.4). Similarly, A/T > 1 (76 versus 40%; P<0.001), blurred margins (52.8 versus 18.8%; P<0.001), solid hypo-echoic appearance on US (80.6 versus 52.4%; P<0.001) and intranodular vascular pattern (type 2) (61.6 versus 49.7%; P<0.001) were significantly more frequent in malignant than in benign nodules.

Conclusions: The data show that no single parameter, including nodule size, satisfactorily identifies a subset of patients to be electively investigated by FNAC. The authors concluded that A/T > 1 with at least two of ultrasound features (microcalcification, blurred margins, hypo-echoic pattern) is today the best compromise between missing cancers and cost-benefit.

COMMENT

Palpable thyroid nodules are found in 4-7% of the population, but as many as 50-70% of subjects with no known history of thyroid disease may have non palpable small nodules, that are usually discovered incidentally by ultrasound examination. The overall risk of malignancy is low (~5%) but it is not negligible. The two recent American & European consensus guidelines on “thyroid nodules and cancer” have underscored the major roles of ultrasound and fine needle aspiration cytology (FNAC) in the diagnosis and management of nodules. FNAC is considered to be the most reliable diagnostic test for thyroid nodules but this technique is operator-dependent and, therefore, the quality of the information gained by FNAC must be judged in the context of this particularity. Many factors intervene in the quality and reliability of the results obtained from FNAC. The best scores are obtained when specialized teams have acquired a large experience (both technically for performing FNA and interpreting cytology). It is stated that an
average of 40-50 procedures/month constitutes a safe limit for acquiring such experience. Also, the best results are obtained when cytologists perform the aspiration and read the smears. Finally, the use of ultrasound-guided FNA is an additional asset that is particularly important for small or partially cystic (or hemorrhagic) nodules.

In the present study, these general notions are confirmed. Out of the 7,455 nodules examined for cytology, 2,865 (38%) were less than 1 cm in diameter and suitable smears for cytology were obtained in 6,135 nodules (82% of the cases). The difference between the nodules examined (N=7,455) and the number of patients (N=4,495) was related to the fact that multiple nodules were present in 1,351 subjects. In the literature, non-diagnostic FNAC range between 10-20% and, in this context, nodule size is an important – albeit not the sole – component of technical failure. In this study, there was a 26% failure rate in the small nodules, i.e. approximately the double compared to the large nodules. The overall percentage of confirmed malignancy in present series was 4.6%. One of the interests of the study was that the analysis of ultrasound characteristics (such as micro-calcifications, blurred margins, hypo-echoic patterns, and intra-nodular vascular flow) confirmed that these characteristics were useful criteria for malignancy. Furthermore, the authors showed that a lesion with a shape taller than wide was another useful criterion of malignancy (O.R.=8.6). Thus in summary, because no single criterion exists to discriminate between benign and suspicious nodular lesions, a compromise is proposed by the authors, namely A/T ≥ 1, with at least two additional ultrasound features. In their experience, the application of this compromise would allow to miss less than 1% of carcinomas. Finally, it should be remembered that the present study is retrospective and, therefore, these conclusions need to be confirmed in a prospective study.

(Daniel Glinoer, M.D.; Ph.D.)

See Table below

| Table 1 Diagnostic value of different ultrasound features and their combination for the identification of malignant thyroid nodules. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Ultrasound features** | **Sensitivity (%)** | **Specificity (%)** | **PPV (%)** | **NPV (%)** | **Performed FNAC (%)** | **Missed carcinomas (%)** |
| (a) Size ≥ 10 mm | 77 | 35 | 5.4 | 97 | 65 | 19 |
| (b) Hypo-echoic* | 81 | 47 | 7.0 | 98 | 53 | 19 |
| (c) Blurred margins* | 53 | 81 | 12.0 | 97 | 19 | 47 |
| (d) Calcifications* | 72 | 71 | 10.8 | 98 | 29 | 28 |
| (e) Vascularity type 2* | 62 | 50 | 5.6 | 96 | 50 | 38 |
| (f) A/T ≥ 1 | 76 | 60 | 8.3 | 98 | 39 | 24 |
| **Derived criteria** | **PPV (%)** | **NPV (%)** | **Performed FNAC (%)** | **Missed carcinomas (%)** |
| A/T ≥ 1 at least two US features (b–d) | 99 | 57 | 6.0 | 99 | 72 | 0.9 |
| Hypo-echoic pattern + at least one US feature (c–e) (ref. 6) | 79 | 61 | 6.8 | 98 | 39 | 23 |

PPV, positive predictive value; NPV, negative predictive value; A/T: anteroposterior/transverse diameter ratio. *see Methods for detail.
ASSAY OF CALCITONIN

Comment interpréter une hypercalcitoninémie ?

Authors: Levy-Bohbot N, Patey M, Larbre H, Hecart A-C, Caron J, Delemer B (Reims, France)


SUMMARY

Propose: Today, calcitonin assay is used for the diagnosis of the medullary cancer of the thyroid (MCT) in the context of nodular thyroid disease. Calcitonin is an excellent marker of MCT but hypercalcitoninemia can also be related to other diseases, such as renal failure, endocrine tumors other MCT and sometimes ‘C’ cell hyperplasia, which is a not well-defined situation. Recent studies have contributed to define calcitoninemia thresholds, with the aims to guide decisions and avoid excessive invasive treatment.

Current knowledge and key points: After a brief reminder of the physiological role and the assays of calcitonin, the difficulties encountered in interpreting the hypercalcitoninemia and its potential causes other than MCT are addressed. Recent studies, on large series, now allow a better knowledge of specificity and sensitivity of calcitonin measurement in patients with nodular thyroid disease and a well-argued management.

Future prospects and projects: In the future, calcitonin dosage will be ordered even more frequently, as some authors recommend it as part of the routine work-up for the diagnosis of a thyroid nodule. It is up to the medical community to delineate how to use this remarkable marker, after considering all possible situations of benign hypercalcitoninemia and reserving aggressive treatments for the patients who really need them.

COMMENT

Calcitonin (CT) is a hormone produced by thyroid parafollicular ‘C’ cells. This peptidic molecule (containing 32 amino acids) has a physiological role in phosphocalcic and bone metabolism. Specific assays for CT (using IRMA, IMA, etc.) allow for the detection of intact monomeric CT with a great accuracy. Based on the studies carried out by the GTE in the last decade (le Groupe Français des Tumeurs Endocrines), a serum CT level of ≤ 10 pg/ml or ≤ 30 pg/ml (after a pentagastrin stimulation test) is considered normal. Above 50 pg/ml (after pentagastrin stimulation), the dosage of CT is clearly considered abnormal. Between 30 and 50 pg/ml (after pentagastrin stimulation), there is a grey zone between a ‘normal’ response and a pathological condition.

In the present review, the authors discuss a number of causes of hypercalcitoninemia outside medullary cancer of the thyroid (MCT). Elevated CT values have been reported in endocrine tumors other than MTC (mainly intestinal tumors). Hypercalcitoninemia also occurs functionally in hypercalcemic patients, conditions with chronic hypergastrinemia (Biermer’s anemia, Zollinger-Ellison syndrome, or after treatment with IPPs), chronic renal failure, and pseudo-hypoparathyroidism (type Ia). The calcitonin ‘precursor’(CTP) is a ubiquitous molecule containing 116
amino-acids, that is not normally found in the serum. However, elevated CTP levels have been found in patients with severe sepsis (bacterial and parasitic infections) and recent data seem to indicate that CTP might possibly interfere with CT measurements. The authors therefore recommend avoiding CT measurements in patients during an infection. Concerning C cell hyperplasia, the authors review the model of familial MCT and discuss the association of abnormally elevated CT levels found in Hashimoto’s thyroiditis and non-medullary thyroid neoplasia. Finally, the authors discuss the controversy as to whether CT measurements ought to be (or not?) a part of the routine work-up of a thyroid nodule. This is an interesting topic for which presently a difference of opinions remains between the recently published American and European consensus for the diagnosis and management of thyroid nodules and cancer. (Daniel Glinoer, M.D.; Ph.D.)

See Figure below

![Diagram showing different types of hyperplasia and neoplasia in the thyroid](image)

SUMMARY

**Background:** A randomized clinical trial was performed to clarify whether the continuous use of methimazole (MMI) during radioiodine therapy (RI\textsuperscript{131}) influences the final outcome of this therapy.

**Design:** Consecutive patients with Graves’ disease (N= 30) or a toxic nodular goiter (N = 45) were rendered euthyroid by MMI and randomized to stop MMI 8 days before RI\textsuperscript{131} (group: ‘-MMI’; n=36) or to continue MMI until 4 weeks RI\textsuperscript{131} (group: ‘+MMI’; n=39). Calculation of the I\textsubscript{131} activity included an assessment of the I\textsubscript{131} half-life and the thyroid volume.

**Results:** The 24-hour thyroid I\textsubscript{131} uptake was lower in the ‘+MMI’ group (44.8 ± 15.6%) than in the ‘-MMI’ group (62.1 ± 9.9%; p<0.001). At 3 weeks after therapy, no significant change in serum free T\textsubscript{4} index was observed in the ‘+MMI’ group (109 ± 106 \textit{versus} 83 ± 28 nmol/L at baseline; P = 0.26), contrasting with an increase in the ‘-MMI’ group (180 ± 110 \textit{versus} 82 ± 26 nmol/L at baseline; P<0.001). The number of cured patients was 17 (44%) and 22 (61%) in the ‘+MMI’ and ‘-MMI’ groups, respectively (P = 0.17). Cured patients tended to have a lower 24-hour thyroid I\textsubscript{131} uptake (50.1 ± 13.8% \textit{versus} 56.4 ± 17.1%; P = 0.09). By adjusting for a possible interfactorial relationship through a regression analysis (variables analyzed: randomization; 24-h and 96-h thyroid uptake; type and duration of disease; age; gender; presence of thyroid antibodies; thyroid volume; dose of MMI), only the continuous use of MMI correlated with treatment failure (P = 0.006) whereas a low thyroid I\textsubscript{131} uptake predicted a better outcome (P = 0.006).

**Conclusion:** Continuous use of methimazole hinders an excessive increase of the thyroid hormones during RI\textsuperscript{131} therapy of hyperthyroid diseases. However, such a strategy seems to reduce the final cure rate, although this adverse effect paradoxically is attenuated by the concomitant reduction of the thyroid I\textsubscript{131} uptake.

COMMENT

Radioiodine (RI\textsuperscript{131}) therapy is widely used for the treatment of hyperthyroidism. A controversy remains regarding the ideal I\textsubscript{131} dose calculation and the use of antithyroid drugs (ATD) in conjunction with RI\textsuperscript{131} therapy. An excellent example of the controversy concerning the I\textsubscript{131} dose calculation can be found in a recent investigation carried out by Marianne Tondeur et al. among the Nuclear Medicine Centers in Belgium (see: Clinical Endocrinology \textbf{65}: 206-209, 2006). Concerning the concomitant use of ATD during (or immediately before) RI\textsuperscript{131} administration, several retrospective studies...
have indicated that ATD reduce the beneficial effects of R\textsubscript{I}\textsuperscript{\textsuperscript{[131]}}. However, these studies might carry the risk of having been influenced by selection biases and, furthermore, recent prospective trials have not confirmed a detrimental effect of ATD. Considering the contradictory results from earlier studies, the authors bravely undertook the present randomized clinical trial. Their results confirmed that the thyroid I\textsubscript{131} uptake was decreased in patients receiving ATD. R\textsubscript{I}\textsuperscript{\textsuperscript{[131]}} undergoes organification in the thyroid gland, and ATD block the organification processes, thereby reducing thyroid uptake. This implies that the half-life or I\textsubscript{131} in the thyroid is altered (i.e. increased) because it is no longer (or less avidly) trapped within the thyroid, probably explaining the decreased cure rate associated with ATD administration during R\textsubscript{I}\textsuperscript{\textsuperscript{[131]}} therapy. The results also confirmed a higher rate of treatment failure in patients receiving ATD. The present trial supports the concept that a greater rate of treatment failure is to be expected when ATD are continued during R\textsubscript{I}\textsuperscript{\textsuperscript{[131]}} therapy. Therefore, either ATD should be withdrawn a few days before R\textsubscript{I}\textsuperscript{\textsuperscript{[131]}} administration (and resumed one to two weeks later when clinically required to control thyrotoxicosis) or the calculated R\textsubscript{I}\textsuperscript{\textsuperscript{[131]}} dose should be adapted in order to account for this detrimental effect of ATD.

(Daniel Glinoer, M.D.; Ph.D.)

See Figure below

![Diagram](image-url)
Title: The association between hypoecchogenicity or irregular echo pattern at thyroid ultrasonography and thyroid function in the general population.


SUMMARY

Objective: Patients with overt hypothyroidism show decreased echogenicity of the thyroid at ultrasonography (US). The aim of the study was to investigate the association between echogenicity of the thyroid/irregular echo pattern, and thyroid function in the general population, i.e. subjects without overt thyroid disease.

Design: A cross-sectional investigation of 4,649 randomly selected adult subjects.

Methods: Blood samples were analysed for serum TSH, thyroid hormones and thyroid autoantibodies. US of the thyroid was performed.

Results: Participants with decreased echogenicity (n=379) had a higher mean serum TSH (1.65 mU/L) compared with subjects with normal echogenicity (1.21 mU/L; P<0.0001). The association was stronger in subjects with markedly decreased echogenicity (4.20 mU/L; P<0.0001). A similar association was seen when the subjects were divided into subgroups according to the level of TSH: more subjects with high levels of TSH had decreased echogenicity (P<0.0001). Likewise, more subjects with high levels of TSH had an irregular echo pattern (P<0.0001). Subjects with decreased echogenicity had a higher risk of having thyroid autoantibodies than subjects without decreased echogenicity (P<0.0001) and this association was stronger when echogenicity was markedly decreased.

Conclusion: The study demonstrated an association between hypoechogenicity at thyroid US and higher levels of serum TSH even in subjects without overt thyroid disease, suggesting decreased echogenicity as an early sign of thyroid dysfunction. Irregular echo pattern, whether accompanied by hypoechogenicity or not, was another possible marker of thyroid failure. This indicates a possible use of thyroid US in detecting early and subclinical thyroid dysfunction.

COMMENT

In clinical practice, one is often confronted with the question of how to define a “preclinical stage” of hypothyroidism. Twenty years ago, the frequent use of the TRH stimulation test was a classical way to assess an exaggerated pituitary response of serum TSH, helping to delineate patients with preclinical hypothyroidism. With the more recent advent of sensitive TSH assays, the TRH stimulation test has been...
largely replaced by the finding of slightly raised serum TSH levels (say between 4-6 mU/L) which has progressively led to the concept of subclinical hypothyroidism (i.e. an abnormal TSH with normal free T4). More recently even, the normal serum TSH range has been revisited, leading some authors to propose to narrow further the truly normal serum TSH range, say from 0.40-4.0 to 0.40-2.5 mU/L. When slight serum TSH abnormalities are encountered, the next question is the etiology of preclinical hypothyroidism. Since thyroid autoimmunity is, by far, the most common cause of subtle thyroid dysfunction, the association of an abnormal serum TSH level with positive thyroid antibodies serves to reinforce the clinical suspicion of an early stage of thyroid underfunction. Similarly, ultrasonography of the thyroid gland (US) often reveals irregular echo patterns and hypoechogetic areas in the gland of patients with chronic thyroid autoimmunity. The main interest of the present population study was to investigate a large group of normal subjects, in order to evaluate the frequencies and associations of abnormal US patterns, presence of thyroid autoantibodies, and thyroid (dys)function. When neither hypoechogeticity nor irregular echo patterns were present in the population, only 2.2% of subjects had subclinical hypothyroidism (SCH), defined herein as a serum TSH above 3.6 mU/L. Conversely, irregular echo patterns alone were found in 5% of SCH patients; hypoechogeticity alone in 12% of SCH patients; and the association of both irregular echo and hypoechogetic patterns at US in 27% of patients with SCH. Furthermore, when participants showed both abnormalities at US examination, positive TPO-Ab was present in almost half of the subjects. Present results indicate that routine US examination is a useful complementary tool to laboratory biochemical data (i.e. TSH, free hormones, autoantibodies) in the early evaluation of thyroid status.

(Daniel Glinoer, M.D.; Ph.D.)

See Figure below
**Summary**

**Objective:** Maternal (subclinical) hypothyroidism during pregnancy is associated with increased morbidity and mortality. Recent guidelines do not advocate universal screening for thyroid function during early pregnancy, but only in well defined ‘high-risk’ pregnant women with a personal or family history of thyroid disorders. The authors wanted to investigate whether selecting a particular group of pregnant women was a good alternative for general screening.

**Design:** Prospective single-centre cohort study.

**Methods:** Thyroid function was assessed with measurements of serum TSH, FT4 and FT3 in 1560 consecutive pregnant women during their first antenatal visit (median gestation time: 9 weeks). The presence of thyroid autoimmunity was assessed by the means of TPO-Ab in 1327 (85%) of them. The high risk group comprised 413 (26.5%) women and the low risk group 1147 (73.5%).

**Results:** Forty (2.6%) of all investigated women had an increased serum TSH (> 4.2 mU/L). This prevalence was higher in the high-risk group (6.8%) versus that in the low-risk group (1%; p<0.0001). Presence of personal history of thyroid disease (R.R. = 12.2; p<0.0001), other autoimmune disorders (R.R. = 4.8; p=0.016), TPOAb (R.R. = 8.4; p<0.0001) and family history of thyroid disorders (R.R. = 3.4; p<0.0001) increased the risk of having a raised TSH. However, 12/40 women (30%) with increased TSH were allocated to the ‘low-risk’ group.

**Conclusions:** When screening for thyroid function was only performed in pregnant women with a high-risk profile, about 30% of women with (subclinical) hypothyroidism were not diagnosed.

**Comment**

Maternal (subclinical) hypothyroidism during early pregnancy has been associated with impaired neuropsychological development of children, adverse outcomes such as premature birth, preeclampsia, breech delivery and increased fetal mortality. The presence of thyroid autoimmunity in euthyroid pregnant women is also a risk factor for (recurrent) first trimester miscarriages. Findings such as those listed above have lead to the proposal of systematically screening pregnant women for thyroid disorders. However before a screening program can be implemented, answers to some fundamental questions should be provided. Firstly, whether the
prevalence of thyroid disease during pregnancy is high enough? Secondly, what is the most reliable screening test? And thirdly, whether intervention strategies have been shown to be safe and effective in decreasing the negative consequences of thyroid disorders before and during pregnancy? A certain number of positive answers to these queries has been provided, but other questions remain unanswered.

The frequency of hypothyroidism in pregnant women is sufficient (2-3%) to warrant screening by measurement of TSH and probably also thyroid antibodies (10-20% during pregnancy). Similarly, an adverse impact of thyroid disorders on both the mother and fetus has clearly been documented. To date, only one randomized prospective intervention trial has been published, showing a significant decrease in the rate of spontaneous miscarriage and preterm delivery in euthyroid women with thyroid autoimmunity treated with l-thyroxine since early gestation. However, universal screening cannot be recommended on the basis of a single trial. In 2005, an international committee was set up and proposed guidelines for “thyroid disorders and pregnancy” and targeted screening for women who are at an increased risk (for instance with diabetes) or having an active thyroid disease.

The aim of present study was to investigate whether a group of pregnant women with thyroid disorders would be missed when screening only high-risk pregnant women. The answer to this question was positive, since the authors showed that although the prevalence of thyroid disorders was clearly higher in the high-risk group, about one-third of women with subclinical hypothyroidism would be missed. In their article, the authors highlighted the notion that when trimester-specific references for TSH would be available (as they calculated them with a post-hoc analysis), the prevalence of increased TSH would even be higher in all pregnant women, even in the high-risk group. Applying references for FT4 adapted to pregnancy could also alleviate the dilemma on the women with a normal TSH and a low FT4. It should also be mentioned that TPO antibodies were measured, with an older agglutination kit. If a more recent test would have been used, the prevalence of thyroid autoimmunity would probably have been even higher in the high-risk group (compared to the low risk group). Another remaining point of discussion concerns the optimal timing for screening, since changes in TPO occur due to immunological adaptations and serum TSH decreases in 20% of women at the end of the first trimester. Until properly randomized controlled trials, including a large number of pregnant women, show a beneficial impact of thyroxine treatment on the outcome of pregnancy, the discussion on the validity of screening will continue.

In summary, when only screening for thyroid function in high-risk pregnant women, an important fraction of pregnant women with subclinical hypothyroidism would be missed. This could be only be resolved by screening all pregnant women. *(Kris Poppe, M.D.; Ph.D.)*