CORRESPONDENCE

Euthyroid Goiter With and Without Nodules—Diagnosis and Treatment

by Prof. Dr. Dr. med. Dagmar Führer, Prof. Dr. Dr. med. Andreas Bockisch, Prof. Dr. med. Kurt Werner Schmid in volume 29–30/2012

A Big Challenge

According to the reported prevalence rates, some 16 million people in Germany are living with thyroid nodules. In spite of a slightly falling trend, this means about 300 affected patients for every GP. This situation presents a big challenge for all general practitioners and specialists in internal medicine who are working in primary care. Rational treatment strategies can be developed only if insights from clinical epidemiology are also taken into account.

We find ourselves confronted with a dilemma: the search for clinically relevant thyroid malignancies is akin to searching for a needle in a haystack. Neither laboratory diagnostics nor optimized thyroid sonography nor scintigraphy nor fine needle aspiration biopsy are suitable for diagnosing thyroid malignancies efficiently, even if the technology is excellent and the associated specificity and sensitivity are high. Owing to the low prevalence and their varying presentation on imaging procedures, the positive predictive values for thyroid malignancies—and this is the crucial issue—are way too low, even after fine needle aspiration biopsy. For each thyroid malignancy found during surgery, 50 patients would have to be operated on unnecessarily (1).

So what is there to be done? To desist from using a diagnostic technique that goes beyond specific history and clinical examination—such as has already been discussed in the US—is undoubtedly thought provoking (2). We should not underestimate, however, that the interventions mentioned in the article cause iatrogenic harms that are quantitatively and qualitatively relevant (3). We need to rethink how to deal with patients with thyroid nodules, and such a rethink would prompt a conclusion that is totally different from that recommended in the article. It would make sense to make transparent the risk probabilities and balance the benefits and risk of medical measures and reach a shared decision with the patient. DOI: 10.3238/arztebl.2013.0068a

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Conflict of interest statement
The author declares that no conflict of interest exists.

Extremely Low Numbers of Cases

A topical CME article (1) should provide guidance that is evidence based. This was often not the case in the article under discussion. An example: The authors say that the serum calcitonin concentration should be measured in every patient with euthyroid nodular goiter, in order to ensure that medullary thyroid carcinoma (MTC) is not missed. Medullary thyroid cancers constitute 7% of all thyroid cancers.

In Germany, 5350 cases of thyroid cancer are diagnosed every year (Robert Koch–Institute, 2010); this translates into 400 cases of MTC. 780 patients die from thyroid cancer, among them 250 from MTC. These are extremely low case numbers compared with other preventable causes of death.

400 cases of MTC have to be seen against 10 million people with nodular goiter (20% of the adult population) who should have their calcitonin measured. This corresponds to 1 patient with MTC in every 25 000 cases of nodular goiter. When conducting investigations with such poor ratios of examined patients to actually affected patients, the result—in contrast to targeted diagnostic evaluation—will always be more false-positive findings than true-positive ones.

This means: Herrmann et al (2) found a prevalence of MTC in their German studies of 0.2%; international rates are comparable (3). When a specificity of calcitonin testing of 95% and a sensitivity of 100% is assumed, the positive predictive value is 4%. This means that on the basis of a positive calcitonin test—even if a pentagastrin-stimulated test is used additionally—25 patients would have to to be operated in order to maybe help one of them. An operation is always necessary since CT and fine needle aspiration biopsy are less exact than the calcitonin test and therefore cannot be used to safely rule out cancer.

All this is not discussed in the article, but—in contrast to international perspectives (3, 4)—the test is recommended as a routine. One might assume that it is up to anybody to make a "recommendation." However, in the context of a CME article, a recommendation becomes binding in a way that should not be underestimated—and can be risky in this setting.

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Poor Sensitivity and Specificity

A CME article published in *Deutsches Ärzteblatt* gives rise to the expectation that it reflects confirmed results. The article by Führer et al. clearly does not meet this expectation. The authors postulate that in every case of a thyroid nodule, scintigraphy should be undertaken at least once. The sensitivity and specificity of this investigation are poor with regard to malignancies (2, 3). It is easy to form an impression of unjustifiably excessive diagnostic testing (seeing that the material that is mass-handled is radioactive). The recommendation to measure calcitonin in every patient with nodular goiter is controversial, to say the least. This recommendation may be appropriate for specialist endocrinology outpatient clinics. For general practice, with its low incidence of thyroid malignancies, it is definitely excessive. The recommendation to measure thyroid antibodies is not sufficiently supported—especially with regard to the relevance of the result for subsequent clinical action. The authors finally recommend a combination of iodine and L-thyroxine. The LISA study cited by the authors (4) investigated iodine and L-thyroxin in isolation as well as in combination. The treated nodules were 1.47–1.96 mL in size. The relative reduction in size by 17.3% therefore corresponded to an absolute reduction of 0.25–0.33 mL—a completely irrelevant order of magnitude. The thyroid volume of 18.2–18.8mL decreased by 1.5 mL, which is similarly irrelevant.

Clinically relevant end points, such as frequency of thyroidectomies or development of thyrotoxicosis, were not studied. The recommendation given in the article is not supported by this study. To publish a CME article full of unconfirmed, not evidence-based, recommendations for maximum diagnostic testing and treatment as a CME article in *Deutsches Ärzteblatt* suggests, in my opinion unjustifiably, that the authors are describing the current gold standard.

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Relevance of Prevalence Values

Regarding the healthcare delivered to patients with euthyroid goiter in general practice, and on the basis of our own research experience in developing a guideline on thyroid disorders in general practice for the German College for General Practitioners and Family Physicians (*Deutsche Gesellschaft für Allgemeinmedizin*, DEGAM), we wish to draw attention to the following.

We have noticed with some surprise that, for some years now, authors of German scientific articles have been citing the Papillon study when reporting the prevalence rates of goiter and thyroid nodules for the German population.

What remains completely unconsidered is the question of the relevance of these prevalence values for the German population. When looking at the selection of the study participants, for example (voluntary participation of "people in work," who themselves (!) reported no prior thyroid-related findings), one may assume a high selection bias. These prevalence rates are not representative for the German population.

Most cases of goiter are asymptomatic. Do all persons with asymptomatic changes of the thyroid (mostly incidental findings) have to be referred for further diagnostic/therapeutic measures? Or is watchful waiting sufficient, provided the patients have received comprehensive information?

It is worth mentioning that thyroid cancer is rare. Estimated, age-standardized incidence rates of thyroid cancer according to the Robert Koch-Institute are 3.1/100 000 in men and 6.3/100 000 in women (1). Most thyroid changes are of benign origin (23).

Against the background of very low incidence rates, the question arises of how effective further diagnostic measures are, especially in cases of asymptomatic euthyroid goiter. Their predictive value is too low due to the very low prevalence rates, especially in general practice.

On the basis of the current state of knowledge, the DEGAM guideline for thyroid disorders will appeal to general practitioners to adopt an approach of watchful waiting in patients with asymptomatic thyroid changes (always depending on the clinical symptoms, in

accordance with patients' own wishes, and provided comprehensive information has been given).

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Conflict of interest statement
The authors are members in the team of authors compiling the DEGAM guideline on the management of thyroid disorders in general practice (currently in development).

Questions Remain Unanswered

Why was the volume reduction owing to combination treatment cited in such detail—where is the benefit for asymptomatic patients? Why was iodine not recommended as first-line treatment?

The standard follow-up interval is set at 6–18 months—why not gradually longer intervals? What is the number needed to screen (NNS) with regard to preventable, high-risk disease courses?

Under the heading "Laboratory tests," you recommend general calcitonin measurements; under "Clinical follow-up and further care after treatment," you write: "History-taking, physical examination, ultrasonography, and TSH measurement generally constitute an adequate clinical follow-up." Is measuring calcitonin therefore useful only in the initial consultation for a nodule? Or in every consultation? What would be the NNS for this measure, and what would be the costs?

In view of the cited prevalence this would involve one-fifth of the adult population. In my opinion, it is not enough to cite guidelines from medical specialty societies in this context. One would expect that in a review article that addresses all doctors, any recommendations would at least briefly have discussed aspects of benefits (NNS) and harms (number needed to harm, NNH).

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Ultrasound-guided Percutaneous Ethanol Injection Was not Mentioned

I wish to add three comments regarding the initiation of prospective studies.

Scintigraphy: the AACE/AME guidelines only ascribe evidence level IV C to this procedure (1). Instead of recommending "baseline scintigraphy" (the radiation exposure is that of some 45 thoracic x-ray films) (2), the gain in diagnostic-therapeutic insights should be questioned (1, 3), so the procedure is not, as a German saying goes, as "unnecessary as a goiter." Routine clinical practice has shown that scintigraphy does not show the majority of sonographically and surgically exposed nodules/cancers and focal autonomies with a size of less than 1–1.5 cm. Without blinded studies of its meaningfulness, the widespread use of scintigraphy should not be promoted.

Measuring calcitonin: the extent to which this should be done in every case of nodular goiter (2) or, in a targeted manner, in sonomorphologically suspect thyroid nodules, in order to detect sporadic medullary thyroid cancer, is—in the absence of prospective studies— the subject of controversy (1, 3, 4). Generalized measurements entail risks and unsettle patients because of technical problems in the laboratory and the many false-positive/false-negative results. Measuring calcitonin in specialized thyroid outpatient clinics with valid laboratory testing facilities and expertise in assessing the result seems a viable alternative (4).

Ultrasound-guided Percutaneous Ethanol Injection/ PEI was not mentioned as the definitive treatment of focal autonomies (1–3). The procedure has been conducted successfully in several thousand patients worldwide and is a routine procedure in intervention centers. Its advantages are a rapid therapeutic effect even after exposure to iodine, cost-effectiveness in the outpatient setting, high acceptability for patients. In unifocal or bifocal autonomies, percutaneous sonography-guided PEI should be discussed with each patient in the interdisciplinary case conference as a low-risk alternative to surgery/radio-iodine treatment. Because of its potential side effects, the procedure should be undertaken in specialized centers with the appropriate expertise (3).

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Professor Braun has received honoraria from the German publishing house Thieme for a book chapter on interventional ultrasonography.

In Reply:

The letters we received in response to our article offer another opportunity to clarify some of the key messages of our CME article.

Unfortunately, only few studies that satisfy the criteria of evidence-based medicine have been conducted for thyroid disorders, although thyroid disease constitutes a very common problem. A comment on NNT/NNH would have been highly desirable but remains impossible due to lack of data and will therefore need to be an objective of future research.

We agree with our correspondents' comments on the low sensitivity and specificity of scintigraphy as a method to detect cancer in patients with thyroid nodules. Thyroid scintigraphy has an altogether different purpose, namely, that of detecting thyroid autonomy, and is an excellent tool for just that. Especially on the background of an ageing population and the frequent exposure to contrast medium during CT scans and cardiac catheterization, the risk of iodine-induced hyperthyroidism due to thyroid autonomy should not be neglected. These insights are also reflected in the 2010 recommendations from AACE/AME/ETA.

Measurement of calcitonin in nodular thyroid disease (thyroid autonomy is the exception) has for many years been included in the European recommendations for the diagnostic evaluation of thyroid nodules (among others the thyroid section of the German Endocrine Society, the European Thyroid Association, AACE/AME/ETA). The notion "controversial" applies to the reluctance among US doctors to use the procedure, which has other reasons than confirmed evidence for the early detection of MTC: e.g. the aspect of cost and, in the past, the unavailability of a stimulation test in the US.

In Germany, one-time measurement of calcitonin in the initial work-up of nodular thyroid disease is a blessing, since it helps to detect MTC at an early stage. Thyroid specialists may advise in situations where interpretation of calcitonin levels is difficult. Operating on a euthyroid nodular goiter without preoperative calcitonin measurement is obsolete in Germany today.

Measuring thyroid autoantibodies is not routinely recommended in patients with nodular goiter . However if ultrasonography has raised the suspicion of autoimmune thyreopathy, measurement of e.g. TPO antibodies may be helpful (1).

The LISA study was conduced over one year; the study design is exemplary and it provides the only recent evidence for Germany, especially on the background of the German tradition of medical treatment of thyroid nodules/nodular goiter. As regards volume reduction, iodine was shown to be inferior to the combination treatment of iodine plus levothyroxine at one-year follow-up. A longer study period for LISA would have been highly desirable, in order to clarify several important aspects of management discussed in the article.

The reported follow-up interval in nodular goiter is controversial, and unfortunately no evidence exists for this either. Thus it is important to make the decision on an individual case basis (size of nodule, risk , probability of developing symptoms). The indication for treatment is naturally defined by balancing potential benefits, and risks. This key message was presented in our article just before the comments on treatment options.

The European and North American recommendations (AACE/AME/ETA) explicitly advise against percutaneous sonography-guided percutaneous alcohol instillation, because:

1. Studies showed recurrent autonomies over time, and
2. The options of radio-iodine treatment or thyroid surgery constitute reliable and safe interventions for the ablation of autonomies.

In selected cases, cysts still do constitute an indication for percutaneous sonography-guided percutaneous alcohol instillation.

We strongly advice against the proposed diagnostic and therapeutic nihilism when dealing with thyroid patients.

To wait for complications and risks would mean ignoring the following aspects:

1. Evidence has shown that thyroid malfunction is common in the general population and is associated with morbidity.
2. Long-term complications may arise from thyroid disorders that for patients and doctors are seemingly asymptomatic.
3. Thyroid autoimmunity is common and relevant in women who wish to start a family.
4. Clinical symptoms of thyroid malignancy indicate a tumor at an already advanced stage.

What is needed is a rational management of thyroid nodular disease, and our review article is intended to provide some decision aids and explanations to this end.

Fortunately, an announcement of "guidelines in development" also provides an opportunity to include corrections. In view of the responsibility for the well-being of patients receiving healthcare from GPs, we sincerely hope that this will be done, and we strongly invite the colleagues involved in guideline development to discuss this issue with the thyroid section of the German Endocrine Society.

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Professor Führer is in receipt of honoraria for consultancy work from AstraZeneca and Pfizer. For continuing medical educational events and conferences she has received travel expenses and honoraria from Merck, Sanofi-Aventis, Ipsen, Pfizer, Novartis Amgen, and Astra-Zeneca. For conducting commissioned clinical studies she has received honoraria from Astra-Zeneca, Pfizer, Ipsen, Novartis, Bayer, Lilly, Novo Nordisk, Merck, and Sanofi-Aventis.