Original article

The DIAGONALE study: A survey designed to analyze the diagnosis and management of goiter in France

Étude DIAGONALE : observatoire du diagnostic du goitre et des pratiques médicales nationales liées à cette pathologie

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Abstract

Objective. – Euthyroid goiter is frequent for general practitioners (GPs) and endocrinologists (ENDOs). It may induce complications especially in elderly subjects when it becomes nodular and hyperfunctional whereas in young subjects prevention of iodine deficiency may prevent this evolution. The primary objective of the observational study diagnosis of iodine deficiency induced goiter and national medical practices (DIAGONALE) was to determine the circumstances of diagnosis of euthyroid goiter, its incidence, the patient characteristics and the management. Methods. – A representative sample of GPs and ENDOs working in a private medical practice (exclusively or not) was randomly drawn from a national file without changing the physician-patient relationship. Results. – Four hundred and sixty-nine GPs and 195 ENDOs participated in the study. Goiter was diagnosed in 0.86% of patients seen by GPs and 15.7% of patients seen by ENDOs. Pregnant women were mainly and teenagers exclusively seen by ENDOs. The interview and clinical examination were an important time in the management of euthyroid goiter. TSH level was systematically assayed as well as an ultrasonography; 22.6% of GPs did not perform a scintigraphy versus 63.1% of ENDOs. Levothyroxine treatment was frequently prescribed and the objective of TSH levels was 2 mU/L for GPs and 1 mU/L for ENDOs. Conclusion. – This observational study showed differences in the management of euthyroid goiter between GPs and ENDOs but also many common practices. It also highlighted a higher incidence rate of goiter in pregnant women and teenagers seen by ENDOs.

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Résumé

Objectif. – Le goitre simple est un problème fréquent pour les médecins généralistes (MG) et les endocrinologues (EC). Il peut conduire à des complications notamment chez le sujet âgé quand il devient nodulaire et hyperfonctionnel. Une prise en charge simple chez le sujet jeune repose sur la prévention de la carence iodée. L’objectif de l’observatoire diagnostique du goitre par carence iodée et des pratiques médicales nationales (DIAGONALE) était de préciser les circonstances de diagnostic du goitre simple, son incidence, les caractéristiques des patients et les différentes prises en charge. Méthodes. – Les données ont été recueillies à partir d’un échantillon représentatif de MG et d’EC libéraux sans modification de la relation médecin–patient. Résultats. – Au total, 469 MG et 195 EC ont participé à l’étude. Le diagnostic de goitre a été posé chez 0,86 % des patients des MG et 15,7 % des patients des EC. Les femmes enceintes étaient vues essentiellement et les adolescentes exclusivement par les EC. L’interrogatoire était un moment important ainsi que l’examen clinique lors de la consultation. Un dosage de TSH était quasiment toujours demandé ainsi qu’une échographie. 63,1 % des EC versus 22,6 % des MG ne demandaient jamais de scintigraphie thyroidienne. L’instauration d’un traitement par lévothyroxine était fréquente, et l’objectif de TSH était de 2 mU/L pour les MG, et 1 mU/L pour les EC. Conclusion. – Des différences et des attitudes communes ont été mises en évidence concernant la prise en charge du goitre simple entre les MG et les EC avec une prise en charge préférentielle du goitre chez la femme enceinte et les adolescents par les EC.

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1. Introduction

Euthyroid goiter (enlargement of the thyroid gland without associated dysthyroidism) is a common finding reported by general practitioners (GPs) and, as would be expected, even more so by endocrinologists (ENDOs). Yet to date no large-scale studies or guidelines have been published for the management of simple euthyroid goiter in France.

In 1999, the World Health Organization (WHO) reported that goiter affects approximately 13% of the world population, i.e. approximately 740 million individuals [1]. Incidence figures have ranged from 5% on the American continent to more than 30% in the Middle-East. In Europe, the condition affects 15% of the population (130 million individuals). Clinically, goiter is assessed by inspection and palpation. Ultrasonography is also useful, despite the inter-observer variability in estimating gland volume [2]. Published studies generally use the values established by the WHO for the upper limit of normal gland volume: 18 ml in females and 25 ml in males [3]. Worldwide, iodine deficiency is the leading cause of euthyroid goiter. Gland enlargement is a physiological adaptation to this deficiency. When iodine intake is insufficient, TSH secretion increases the activity of the iodine/sodium symporter, which in turn increases the proportion of absorbed iodine directed to the thyroid gland. This proportion can change from less than 10% with optimal iodine intake to more than 80% in case of iodine deficiency [4]. TSH stimulates thyroid cell hypertrophy and hyperplasia. Initially, the goiter is diffuse and homogeneous, the gland starting to enlarge early during puberty or pregnancy in predisposed persons [5]. At this stage, the process remains reversible, but with time nodules can develop leading to multinodular goiter with a risk of hyperfunction and toxicity in older adults. The risk of comorbid conditions, particularly heart disease at this age, may require fine-tuned management. Preventive measures, notably adequate iodine intake, are crucial. If such measures are unfeasible, appropriate treatment should be started early, generally at puberty when the condition remains reversible.

Among the therapeutic options, levothyroxine is the mainstay treatment for simple goiter. Levothyroxine is also indicated after surgery to remove a large potentially compressive goiter [6] or after radioiodine therapy for toxic or hyperfunctional goiter.

Considering the lack of sufficient data concerning current management practices for simple goiter in France, we conducted a large-scale observational study, diagnosis of iodine deficiency induced goiter and national medical practices (DIAGONALE) to determine the incidence of euthyroid goiter in France and ascertain the characteristic patient features and current therapeutic practices. The secondary objective of the study was to estimate the annual incidence of euthyroid goiter and toxic nodular goiter in France.

2. Methods

A sample of GPs and ENDOs working in a private medical practice (exclusively or not) was randomly selected from a national database of practicing physicians who had agreed in principle to participate in observational studies. The sample was designed to be representative of the GP and ENDO population in France.

For this observational study, the physicians were asked to recall their medical practices over the past year. The data collected did not concern individual patients and had no impact on the patient-doctor relationship. The practicing physicians made all therapeutic decisions independently.

The sampling process was designed to create an observer-physician population representative of the national geographic, gender and age distributions of GPs and ENDOs practicing in France as described in the national report no. 88 published by the Direction of research studies, evaluation and statistics (DREES) in October 2005 [7]. The goal was to include 750 GPs and 250 ENDOs.

During the course of the survey, observer-physicians were asked to provide information concerning their personal status and the incidence of euthyroid goiter among their patients, with the type of patients and the circumstances of diagnosis. For management practices, the observer-physicians were asked to respond to a series of questions with standardized responses: always; sometimes; never. The questions concerned history taking, physical examination and complementary tests performed during the past year. Continuous variables were expressed as mean±standard deviation or percentage, with 95% confidence interval as appropriate.

3. Results

3.1. Observer physicians

Among the physicians solicited for the study, 784 GPs and 244 ENDOs agreed to participate in the observational study; 469 GPs (60%) and 195 ENDOs (80%) actually participated and estimated they had seen 3283 ± 2479 and 1911 ± 1009 patients, respectively, during the past year. Mean age of the observer physicians was 49.6 ± 7.4 years (50.2 ± 5.3 for GPs and 48.0 ± 7.5 for ENDOs). The observer physicians were older than the DREES population; this phenomenon was more marked for the GPs than for the ENDOs. The proportion of men was 83.8% for GPs and 29.7% for ENDOs (DREES data 2005: 61.6% and 32.6% respectively). Among the ENDOs, 52.9% worked in a private practice exclusively and 47.1% had a mixed practice (hospital and private practice). The geographic distribution was comparable to the population described in the DREES 2005 report (data not shown).

Besides the specialty of the observer physician, age had an effect on the number of diagnoses of goiter since the incidence increased 6% for each 10 years of age.

3.2. Goiter incidence

The diagnosis of goiter was established in 0.86% of the GPs’ patients (mostly simple euthyroid goiter) and 15.7% of the ENDOs’ patients (mostly nodular euthyroid goiter). Distribution by type of goiter is presented in Table 1. Female gender predominated. Most of the pregnant women and adolescent girls were seen by ENDOs (Fig. 1). Considering the geographic
distribution, the incidence of simple goiter was higher in mountainous regions (×2.3, P<0.0001), urban areas (×1.3, P<0.0001), and central and eastern France (×1.3, P<0.05) compared with the sample mean.

The diagnosis of simple goiter was established under the following circumstances: systematic physical examination (39.4% and 20.6% for GPs and ENDOs respectively); signs of thyroid dysfunction (13.8% and 7.3%); physical signs (apparent goiter or local discomfort) (20.6% and 12.1%). Data were missing for approximately 18% of GPs and ENDOs and among the ENDOs, 47% of the circumstances of diagnosis had been established by another physician. These figures were changed little by excluding pregnant women. In adolescent girls, the corresponding figures were for GPs and ENDOs respectively: 43.7% and 21.0%; 11.1% and 9.1%; 23.8% and 18.1%.

More than half of patients (53%) seen by ENDOs for simple goiter had been referred by other physicians: 31% by GPs, 12.1% by gynecologists, and 9.6% by specialists in occupational medicine or maternal and infantile protection. Excluding pregnant women, these figures were 27.2%, 7.3% and 12.5% respectively. Among pregnant women seen by ENDOs for simple goiter, 23.1% were referred by GPs and 40.2% by gynecologists. Among adolescent girls seen by ENDOs for simple goiter, 62.2% were referred by GPs, 12.6% by school physicians or specialists in maternal and infantile protection and 6.7% by pediatricians (although the present survey included fewer than 1200 adolescent girls, i.e. less than 7% of patients in the sample population). There were 179 children aged less than 10 years (16 seen by GPs and 163 by ENDOs), certainly corresponding to a very low incidence in children and/or management by pediatricians.

### Table 1

<table>
<thead>
<tr>
<th>Criteria</th>
<th>GP practice (n = 1,418,087)</th>
<th>ENDO pratice (n = 1,418,087)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple euthyroid goiter</td>
<td>6,356 – 0.45% [0.44; 0.46]</td>
<td>10,892 – 3.10% [3.04; 3.15]</td>
</tr>
<tr>
<td>Nodular euthyroid goiter</td>
<td>3,873 – 0.27% [0.26; 0.28]</td>
<td>31,638 – 9.00% [8.90; 9.09]</td>
</tr>
<tr>
<td>Nodular toxic goiter</td>
<td>828 – 0.06% [0.05; 0.06]</td>
<td>8,793 – 2.50% [2.45; 2.55]</td>
</tr>
<tr>
<td>Unclassified goiter</td>
<td>1,074 – 0.08% [0.07; 0.08]</td>
<td>3,874 – 1.10% [1.07; 1.14]</td>
</tr>
</tbody>
</table>

### 3.3. Medical practices during visits for goiter

History taking was an important part of the management practices for simple goiter. Family and personal history of thyroid disease was collected systematically by 86.1% of GPs and 100% of ENDOs. Other elements the physicians looked for included smoking (69.2% versus 78.5% for GPs and ENDOs respectively), regional or ethnic background (41.9% versus 62.1%), injection of iodine contrast agent (39.1% versus 62.6%), and treatment with a lithium-containing product (31.6% versus 63.1%), with a difference in favor of the ENDOs for all items (P<0.01). Conversely, search for treatment with amiodarone was performed similarly by GPs (70.9%) and ENDOs (76.4%). Systematic search for use of iodinated salt and daily intake of fish or seafood was limited but comparable between GPs (21.2% and 24.2% respectively) and ENDOs (20.2% and 20.2%). A similar finding was noted for data collection on nutritional supplements (15.4% for GPs and 22.1% for ENDOs) although this point was less often neglected by ENDOs (P<0.01).

Palpation was almost always performed (98.3% for GPs and 100.0% for ENDOs). The difference was non-significant. Similarly, there was no significant difference concerning estimated goiter size or neck diameter measurements (data collected respectively by 22.9% and 31.2% of GPs and 28.2% and 26.7% of ENDOs). Conversely, ENDOs noted the gross structure (homogeneous nor not) of the goiter more generally (99.0%) than GPs (82.9%) (P<0.001). The same was found for gland consistency (96.9% versus 81.6%, P<0.001).

For complementary tests, TSH assay was ordered almost always (99.2% for GPs and 99.5% for ENDOs). For antithyroglobulin antibodies (TPO) however, practices differed significantly (38.4% for GPs and 56.4% for ENDOs, P<0.001). GPs ordered other explorations more often: free T4 (54.2% versus 32.3% respectively for GPs and ENDOs, P<0.01); thyroid ultrasound (89.1% versus 77.4%, P<0.001); radioiodine scan (12.6% versus 5.0%, P<0.001). A very small proportion of physicians never requested ultrasound explorations (0.2% of GPs and 0.5% of ENDOs) whereas the percentage of physicians who never requested radioiodine scans depended on the type of practice (2.6% for GPs and 63.1% for ENDOs).

In Fig. 2, globally, GPs ordered more complementary tests than ENDOs, for instance the percentage of GPs ordering more than three complementary tests was higher than the corresponding percentage of ENDOs (31.8% versus 25.1%).

Among the GPs, 28.6% always referred their goiter patients to an ENDO (3.9% never). Surveillance was almost constant for all practitioners (92.1% for GPs and 85.1% for ENDOs). Institution of a treatment using levothyroxine was common, but
23.9% of GPs and 3.1% of ENDOs responded they “never” instituted treatment ($P < 0.01$). When a treatment was given, 14.9% of GPs and 3.7% of ENDOs stated they “never” set a TSH objective ($P < 0.01$). Abstention from surgery was more common among ENDOs than GPs (32.1% versus 43.3% for ENDOs) ($P < 0.05$). If surgery was performed, postoperative surveillance was almost always undertaken (91.1% for GPs and 91.8% for ENDOs) although a postoperative treatment with levothyroxine was much less common for GPs (44.0% versus 79.1% for ENDOs) ($P < 0.001$) and 23.4% of GPs (0.9% of ENDOs) “never” set TSH objectives.

When a treatment was prescribed, levothyroxine was used by 98% of the physicians (Table 2). The median TSH objective set by the physicians was 2 mU/L for GPs and 1 mU/L for ENDOs.

The GPs with a higher reported rate of goiter diagnosis (above the average for GPs) were more often women (OR = 2.0, $P = 0.014$), asked more systematically about using iodinated table salt (OR = 1.7, $P = 0.038$) and stated they referred goiter patients to ENDOs “sometimes” rather than “always” (OR = 1.8, $P = 0.010$). Among the ENDOs, those reporting a higher incidence of goiter (above the average for ENDOs) estimated goiter size by palpation “sometimes” rather than “always” (OR = 3.6, $P = 0.016$) and instituted levothyroxine treatment “always” more often than “sometimes” (OR = 4.2, $P = 0.011$).

4. Discussion

The sample of observer-physicians who participated in the DIAGONALE survey were representative of the physician population in France, even though they were older than the physicians described in the DRESS 2005 report, taking into consideration the current aging trend of the medical population in France [8].

The incidence of simple goiter was nearly 7-fold higher in patients seen by ENDOs (3.1%) than by GPs (0.4%). The difference was even greater for nodular goiter: 11.5% of patients consulting an ENDO and 0.33% of those consulting a GP. This difference was probably related to fear of thyroid dysfunction or cancer, which is always evoked in case of a nodular goiter [9] and more generally leads to a specialist consultation.

For GPs, diagnosis generally arose from a systematic physical examination (in about 40% of cases); other circumstances of discovery were the presence of physical signs, followed by signs of thyroid dysfunction. The circumstances of discovery ranked similarly for ENDOs, but with lower percentages since patients were often referred after the diagnosis had already been made by a GP or another physician. Patients were referred to ENDOs for the management of particular situations, for instance pregnancy or goiter in an adolescent girl.

Data collected during history taking showed that physicians were aware of the classical causes of goiter which include past history (family or personal history of thyroid and/or autoimmune disease), smoking [10] and iatrogenic causes. GPs however questioned their patients less about dietary iodine intake (use of iodinated salt) or nutritional supplementation.

GPs and ENDOs almost always palpated the goiter, with a generally very precise qualification of the consistency and nodular or homogenous nature of the gland by ENDOs. A finding probably related to experience. Fewer physicians however noted the neck circumference or the size of the goiter, probably because of the widespread use of ultrasound as the reference exploration to confirm the diagnosis, to identify nodules, which cannot be palpated (due to size and/or localization), and for follow-up. It has been demonstrated that compared with simple palpation, referring patients for ultrasound impacts management of nodular goiter [11]. A radioiodine scan was requested more commonly by GPs than ENDOs who applied the principle that a radioiodine scan should only be performed if the TSH level is below normal [12].

As a rule, GPs prescribed a greater number of complementary tests than ENDOs, although the analysis of variance demonstrated that the real factor was that older physicians prescribed more. It can however be noted that free T4 assay was requested more frequently by GPs and that TSH assay was almost always requested by all physicians. Anti-TPO antibodies were however assayed more commonly by ENDOs looking for an autoimmune context which becomes increasingly prevalent with age, particularly in women [13].

Considering the management practices proposed for simple goiter, abstention from surgery was the rule for 32.1% of GPs and 43.3% of ENDOs, noting that this should be the rule for simple goiter except for potentially life-threatening suspect goiter or very large goiter [14] which in France is basically historical. The usual attitude is to propose regular surveillance or treatment with levothyroxine. Studies such as the Su.VI.MAX survey [10] have demonstrated a negative correlation between the size of the thyroid gland and urinary iodine. Iodine supplementation remains nevertheless a problem in France due to the absence of an adapted and reimbursed formulation. Levothyroxine is usually prescribed to obtain a TSH level around 1 mU/L, and in any case at a dose low enough to avoid secondary cardiac or bone effects, particularly in menopause.

Several particular situations should be discussed for the management of simple goiter. The first is pregnancy. Goiter in a pregnant woman is suggestive of deficient iodine intake and as such can be associated with a significantly higher risk of neuropsychomotor developmental disorders in the child [15].
Type of treatment given for the management of euthyroid goiter by general practitioners (GP) and endocrinologists (ENDO).

<table>
<thead>
<tr>
<th>Patients treated n – % [95%CI]</th>
<th>GP (n = 353)</th>
<th>ENDO (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT4</td>
<td>313 – 88.67% [85.36; 91.98]</td>
<td>170 – 92.39% [88.56; 96.22]</td>
</tr>
<tr>
<td>Iodine supplementation</td>
<td>8 – 2.27% [0.71; 3.82]</td>
<td>3 – 1.63% [0.00; 3.46]</td>
</tr>
<tr>
<td>LT4 + Iodine supplementation</td>
<td>32 – 9.07% [6.07; 12.06]</td>
<td>11 – 5.98% [2.55; 9.40]</td>
</tr>
</tbody>
</table>

Gynecologists are well aware of this problem since 40% of pregnant women seen by ENDOs for goiter were referred by gynecologists. Special care is required to ensure sufficient iodine intake during pregnancy in order to avoid these maternal and fetal consequences [16,17].

Children and adolescent girls may make up less than 8% of the population seen by GPs. In adolescents, goiter may be the first sign of dysthyroidism, often resulting from an autoimmune cause [18]. If the adolescent is euthyroid, the discovery of a goiter generally leads to effective prevention of later progression with levothyroxine and institution of a surveillance schedule [19]. Younger children (<10 years) with goiter have a risk of dysthyroidism-related developmental disorders [5] and consequently are most often seen by ENDOs. It can be recalled that in 1996, the incidence of goiter in the 6–14 age group was 4.1% for boys and 3.1% for girls [20], reflecting the absence of iodine deficiency in this age group. Appropriate care is particularly important for children who develop goiter at this age when it is still potentially reversible. Inversely, goiter diagnosed in elderly patients often raises problems related to thyroid volume and/or dysfunction. In this situation treatment with surgery or radioactive iodine is often required with a definitive treatment with levothyroxine.

This survey has some limitations. First, the degree of iodine deficiency potentially present is unknown, urinary iodine being almost never assayed in routine practice for simple goiter. Consequently, it is difficult to dissociate iodine deficiency goiter from other potential causes. Nevertheless, the geographic distribution in this observational survey, where goiters were found to be more common in regions of eastern France, is consistent with the observation of more marked iodine deficiency in these regions in the SU. VI.MAX study [21]. Another important limitation is the fact that the data collected were not direct observations but an overall evaluation made by physicians recalling their own practices over the past year. More precise data collection would imply a prospective national survey, which might use the DIAGONALE survey as a base.

## 5. Conclusion

DIAGONALE is the first study involving a very large number of practitioners reporting first-line real-life management practices for simple goiter in France. The results must however be interpreted with precaution due to the lack of individualized patient data. Nevertheless, this observational survey has highlighted differences in management practices for simple goiter between GPs and ENDOs, and also points out several common practices. It has demonstrated a higher incidence of goiter among patients seen by ENDOs and a female predominance in the attending population.

### Disclosure of interest

P. Caron consultant for Merck Serono, P. Leherit consultant for Merck Serono, S. Picard consultant for Merck Serono, F. Landron employee of Merck Serono.

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