tion of medical and nursing care, and nutritional intervention, which have improved the survival rate in this most challenging group of patients from 60% to 88%. This has been achieved with good quality of life despite a high perioperative morbidity and the greater technical difficulties related to the small size of the patient.

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Radioiodine treatment of multinodular non-toxic goitre

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Abstract

Objective—To investigate the long term effect of radioactive iodine on thyroid function and size in patients with non-toxic multinodular goitre.

Design—Consecutive patients with multinodular non-toxic goitre selected for radioactive iodine treatment and followed for a minimum of 12 months (median 48 months) after an intended dose of 3.7 MBq/g thyroid tissue corrected to a 100% uptake of iodine-131 in 24 hours.

Patients—69 patients with a growing multinodular non-toxic goitre causing local compression symptoms or cosmetic inconveniences. The treatment was chosen because of a high operative risk, previous thyroidectomy, or refusal to be operated on.

Main outcome measurements—Standard thyroid function variables and ultrasonically determined thyroid volume before treatment as well as 1, 2, 3, 6, and 12 months after treatment and then once a year.

Results—56 patients were treated with a single dose of ¹³¹I, 12 with two doses, and one with four doses. In 45 patients treated with one dose and remaining euthyroid the median thyroid volume was reduced from 73 (interquartile range 50-106) ml to 29 (23-48) ml at 24 months in the 39 patients in whom this was measured during follow up. The median reduction was 40 (22-48) ml (60% reduction, $p < 0.0001$), half of which occurred within three months. Patients treated with two doses as well as those developing hypothyroidism and hyperthyroidism had a significant reduction in thyroid

volume. Eleven patients developed hypothyroidism (cumulative five year risk 22%, 95% confidence interval 4.8% to 38.4%). Side effects were few: three cases of hyperthyroidism and two cases of radiation thyroiditis. Only one patient was dissatisfied with the result; she was referred for operation six months after treatment.

Conclusions—A substantial reduction in thyroid volume accompanied by a low incidence of hypothyroidism and few side effects makes the use of radioactive iodine an attractive alternative to surgery in selected cases of non-toxic multinodular goitre.

Introduction

The yearly growth rate of non-toxic multinodular goitres has been estimated at 10-20%.¹ Suppressive treatment with thyroxine or triiodothyronine reduces the thyroid volume in diffuse non-toxic goitre by up to 30%,² but it is disputed whether such an effect can be achieved in multinodular glands.^{1,3,4} The growing nodular non-toxic goitre is traditionally treated by subtotal thyroidectomy.

At least 10% of patients have a recurrence after subtotal thyroidectomy for non-toxic multinodular goitre.^{5,6} In these patients, as well as in others with a high surgical risk, a non-operative reduction in thyroid size would be desirable. Treatment of hyperthyroidism with radioactive iodine (¹³¹I) is well accepted and usually results in a substantial decrease in the size of the thyroid.^{7,8} The possibility of ¹³¹I treatment of non-

toxic multinodular goitre is less accepted, but recently we found a 41% reduction in ultrasonically determined thyroid volume within one year of treating such patients with ^{131}I .⁹ The present study investigated the long term consequences of ^{131}I treatment on thyroid function and thyroid volume in a large group of patients with non-toxic multinodular goitre to clarify the future role of this treatment.

Patients and methods

Sixty nine patients (62 women) with multinodular non-toxic goitre selected for radioactive iodine treatment during the period 1981-91 were followed for a minimum of 12 months. Median age was 57 (range 30-83) years and all patients had a multinodular goitre on technetium-99m thyroid scanning. The indication for treatment was a growing multinodular goitre, assessed clinically or by ultrasonography on at least two visits, causing either local compression symptoms or—in a few cases—cosmetic inconvenience. This treatment was chosen owing to a high operative risk (cardiac or pulmonary disease, or both), previous thyroidectomy, or refusal to be operated on. None of our patients was pregnant or contemplated further pregnancies at the time of selection for treatment. Of the 13 patients who had had a thyroidectomy, nine had been operated on once, three twice, and one three times.

We intended to give ^{131}I at a dose of 3.7 MBq (100 μCi) per gram of total thyroid mass corrected to a 100% uptake of ^{131}I in 24 hours. In some cases—for example, a goitre of 200 g with an ^{131}I uptake of 20% in 24 hours—this would have meant giving large (3700 MBq (100 mCi)) single doses. For several reasons, including local irradiation protocol, a maximum single dose of 1110 MBq (30 mCi) was chosen. Consequently, 18 of the largest glands were given a lower dose (<3.7 MBq/g thyroid tissue) than intended.

Pretreatment, a $^{99\text{m}}\text{Tc}$ thyroid scan, was performed in all patients with a gamma camera, using 3 mCi $^{99\text{m}}\text{Tc}$ -pertechnetate. Serum concentrations of thyroxine (normal range 59-129 nmol/l) and triiodothyronine (normal range 1.0-2.5 nmol/l) and a triiodothyronine resin uptake test (normal range 0.80-1.25 arbitrary units) were determined by in house methods (assay variation was 6%, 10%, and 5% respectively). Free thyroxine index and free triiodothyronine index were calculated as the total hormone concentration times the resin uptake and given in arbitrary units. Serum concentration of thyroid stimulating hormone was determined, up to 1986, by a previously described radioimmunoassay.¹⁰ From 1986 to 1989 we used an immunoradiometric assay (Boots-Celltech, England) with an intra-assay coefficient of variation of 2.3-4.7% and a detection limit of 0.03 mU/l. From 1989 we used the Delfia hTSH assay (Wallac, Turku, Finland), which has an intra-assay coefficient of variation of 3.7-5.4% and a detection limit of 0.03 mU/l.

Hyperthyroidism was defined as a subnormal serum concentration of thyroid stimulating hormone with a concomitant increase in serum concentration of thyroxine or triiodothyronine, or both. Hypothyroidism was defined as a raised serum thyroid stimulating hormone concentration concomitant with a decrease in free thyroxine index. Patients with raised serum thyroid stimulating hormone concentrations but normal free thyroxine index were classified as having compensated hypothyroidism (seven of 11 hypothyroid patients). These patients were treated with levothyroxine for subjective complaints compatible with hypothyroidism (mainly weight gain) and increasing serum thyroid stimulating hormone concentrations. In the statistical analysis and in the results section these patients were classed as hypothyroid.

Ultrasonic scanning and calculation of total thyroid volume (normal range 9.6-27.6 ml) were performed as previously described¹⁰ with a compound scanner (type 1846, Bruel and Kjaer, Naerum, Denmark). The method in essence comprises obtaining transverse scans of the thyroid with 5 mm intervals from caudal to cranial with the patient supine with hyperextension of the neck. The outline of the gland on the screen of the monitor can be digitised with a light pen connected to a computer for calculation of the surface of one outline and the volume between two successive transverse scans. The sum of all partial volumes equals the total thyroid volume. The average inaccuracy of this method is 7% without any consistent overestimation or underestimation.¹⁰ The mean interobserver variation is 5%¹⁰ and the mean intraobserver variation is 5%.¹¹

Thyroid function variables and the size of the thyroid on ultrasonography were determined before treatment as well as one, two, three, six, and 12 months after treatment and thereafter once every year. Informed consent was obtained from all patients.

Ten subjects (all women) with a median age of 60 (range 46-83) years and an initial thyroid volume of 45 (25-161) ml need special mention. All were treated with one dose of ^{131}I . Follow up data on thyroid volume were not available for these women, but several developed hypothyroidism. So that the prevalence of hypothyroidism would not be underestimated these patients were included. Six of the 10 patients were euthyroid when lost to follow up. Of these six, two patients died of unrelated reasons at age 80 and 85, three years and one year, respectively, after ^{131}I treatment. One patient emigrated, and two were referred back to their private practitioners after 12 and 24 months. One patient was dissatisfied with the effect of treatment and was referred for operation six months after treatment; at this time the initial thyroid volume of 30 ml was unchanged and she was euthyroid. The remaining four of the 10 patients were treated with levothyroxine—three because of compensated hypothyroidism—within 12 months of treatment and referred back to their private practitioner.

STATISTICAL EVALUATION

When calculating the incidence of hypothyroidism we used life table analysis. Longitudinal changes in thyroid gland volume were analysed by the Page test for trend.¹² Because of the lack of volume estimations from different patients at different times, one value obtained before and two values obtained after ^{131}I treatment were used for this test. The values after treatment were the average of the results from six and 12 months, and 24 and 36 months. When both values were missing the patient was excluded from the Page test evaluation, and when only one value was available this value was used. Significance level was chosen at $p < 0.05$.

Results

Median initial thyroid volume in the 69 patients was 74 (range 21-296). All patients were clinically and biochemically euthyroid, but in 21 patients serum thyroid stimulating hormone concentrations were subnormal (<0.4 mU/l).

Fifty six patients (51 women) were treated with a single ^{131}I dose and were followed for a median of 60 (12-120) months. Median ^{131}I dose was 555 (148-1110) MBq. Ten of these patients received a lower dose than intended. Forty five patients remained euthyroid during the follow up period. In the 39 patients in whom it was measured, median thyroid volume decreased gradually from 73 (interquartile range 50-106) to 29 (23-48) ml after 24 months (60% reduction, $p < 0.0001$). Thereafter no significant alterations in

FIG 1—Median changes in thyroid volume alterations after iodine-131 treatment in 39 patients with non-toxic multinodular goitre who remained euthyroid after a single dose. Bars are quartiles

FIG 2—Changes in thyroid volume in five patients (●—●) developing hypothyroidism after one dose of iodine-131 and two patients developing hypothyroidism after two doses given for non-toxic multinodular goitre (○—○). Arrow indicates time of second dose; box indicates diagnosis of hypothyroidism or thyroxine substitution (or both)

thyroid volume occurred (fig 1). Within this period thyroid size was normalised in 19 of the 39 patients (49%).

Nine patients developed hypothyroidism after a median of six (range 3–36) months. Median ^{131}I dose was 474 MBq (296–1110) and thyroid volume was reduced from a median of 48 (28–93) ml to 15 (8–71) ml (69% decrease, $p < 0.05$) in the five patients in whom it was measured (fig 2). Five of these patients had compensated hypothyroidism with normal free thyroxine index and raised serum thyroid stimulating hormone concentrations (7, 12, 16, 27, and 29 mU/l).

Two patients developed hyperthyroidism three months after ^{131}I treatment. Both were treated with antithyroid drugs for several months and thereafter remained euthyroid. Figure 3 shows thyroid volumes. Neither patient had a family history of Graves' disease or other thyroid disorders, but antibodies to thyroid stimulating hormone receptor and thyroid peroxidase were not measured, so evidence for or against Graves' disease cannot be provided.

Twelve patients were treated with a second dose of ^{131}I , mainly to reduce thyroid volume further. They were followed for a median of 48 (12–72) months from the first treatment, with a median of 12 (2–24) months between the two treatments. Median initial ^{131}I dose was 611 (252–925) MBq, and the median second dose was 740 (222–925) MBq. Seven of these patients

received a lower initial dose than intended. Nine patients remained euthyroid during the follow up period. In these patients the initial ^{131}I dose reduced thyroid volume from 90 (34–296) ml to 84 (25–223) ml ($p < 0.05$) and the second dose reduced thyroid volume from 84 (25–223) ml to 69 (11–130) ml ($p < 0.0005$; fig 4). Within the observation period thyroid size was normalised in one patient.

One patient developed permanent hypothyroidism 16 months after and another 24 months after the second ^{131}I dose. Figure 2 gives thyroid volume data. Both patients had compensated hypothyroidism with serum thyroid stimulating hormone concentrations of 7 and 11 mU/l.

One patient developed hyperthyroidism one month after the initial ^{131}I dose and was treated with anti-thyroid drugs for 10 months. Thereafter another ^{131}I dose was given and the patient has been euthyroid since. Figure 3 gives thyroid volume data.

One patient received four doses of ^{131}I (800, 555, 555, and 740 MBq); thyroid volume decreased from 96 ml to 56 ml and the patient has remained euthyroid (fig 4).

During the observation period 11 of 69 patients (16%) developed hypothyroidism. Life table analysis showed a risk of hypothyroidism 60 months after treatment of 22% (95% confidence interval 4–8% to 38.4%; fig 5).

SIDE EFFECTS

Eleven patients developed hypothyroidism. Three patients developed hyperthyroidism and needed drug treatment; one of these patients required repeat ^{131}I

FIG 3—Changes in thyroid volume in three patients developing hyperthyroidism after iodine-131 treatment of non-toxic multinodular goitre. Arrow indicates time of second dose; box indicates diagnosis of hyperthyroidism

FIG 4—Changes in thyroid volume in nine patients remaining euthyroid after two doses and one patient after four doses of iodine-131 for non-toxic multinodular goitre. Arrows indicate times of additional doses

FIG 5—Life table analysis of risk of hypothyroidism during 60 months follow up after treatment of non-toxic goitre with iodine-131. Hatched area indicates risk for patients receiving levothyroxine for decompensated hypothyroidism; solid area indicates risk for patients receiving levothyroxine for compensated hypothyroidism (normal serum thyroxine but raised serum thyrotropin concentrations)

treatment; none of these patients developed hypothyroidism. Two patients had a transient (8 weeks and 12 weeks) episode of radiation induced thyroiditis characterised by mild thyrotoxicosis and anterior neck tenderness; one needed steroid treatment. None of the five patients with test results showing an increase in thyroid function had an increase in thyroid volume. We encountered no cases of exacerbation of obstructive symptoms, and only one of the patients has been referred for thyroidectomy.

Discussion

Sporadic and—in countries with relatively low daily iodine intake—endemic goitre is a fairly common condition. In Denmark, where there is a low to borderline iodine intake of 50–80 µg/day,^{13,14} a minimum of 5% of the adult population is estimated to have a multinodular non-toxic goitre.¹⁰ Thyroid suppression with thyroxine or triiodothyronine, effective at least transiently in diffuse non-toxic goitre,² is probably without lasting benefit in multinodular goitre.¹⁵ Spontaneous reduction in goitre size is unlikely; on the contrary, an average yearly growth rate of up to 20% is to be expected.¹ Surgery is effective and rapidly relieves pressure related symptoms, but goitre recurs in at least 10–15% of patients,^{5,6} the number depending on definition and length of follow up but probably independent of whether thyroxine is given after operation.⁷ Reoperation for whatever indication increases the probability of complications, particularly hypoparathyroidism and laryngeal nerve damage.^{15,16} The larger the glands the more likely the operative complications. Furthermore, many patients with large multinodular goitres are elderly, and surgery may be contraindicated by other medical conditions. Additionally, a number of patients refuse to be operated on. In this light we sought to evaluate the long term outcome of ¹³¹I treatment for non-toxic multinodular goitre.

EFFECT ON THYROID VOLUME

This longitudinal prospective long term study comprising 69 patients showed an overall decrease of 34% in ultrasonically determined thyroid volume after ¹³¹I treatment after 12 months and 55% after 24 months. As the expected spontaneous growth rate is 10–20% a year,¹ the reduction could well be even more pronounced. Most patients were treated with one dose of ¹³¹I, and half of the achievable thyroid volume reduction of 60% (at 24 months) occurred within three months of treatment. Patients offered repeat treatment showed a reduction in volume after the first ¹³¹I dose; a second dose was generally given when the initial volume reduction was inadequate, mostly in patients in whom the first dose was lower than intended due to large glands or a low uptake of ¹³¹I. Patients with

thyroiditis and hyperthyroidism did not have an increase in thyroid volume. Generally the reduction was of the same order in these patients as that seen after ¹³¹I treatment in toxic multinodular goitre.⁷ Other researchers who have shown reductions in goitre size after ¹³¹I treatment in patients with multinodular goitre have used less accurate methods (palpation, neck circumference, and scintigraphy) and scantier observations.^{17–20}

Although 10 of the 59 patients had a small increase in thyroid volume within the first month this in no case caused an exacerbation of obstructive or other symptoms. Surprisingly, 20 patients had normal or only slightly increased thyroid volume (< 50 ml) before treatment, but this is in part explained by recurrence of a unilateral symptomatic goitre in patients with a previous hemithyroidectomy. The average reduction in thyroid volume was independent of initial size of the thyroid. This is not surprising since the dose of ¹³¹I was adjusted for thyroid size.

SIDE EFFECTS

The cumulative risk of hypothyroidism five years after ¹³¹I treatment was 22%, very different from the risk of 100% after eight years observed by Verelst *et al.*²⁰ and the 1.6% found by Keiderling *et al.*¹⁷ These differences and the lack of a relation between ¹³¹I dose and subsequent development of hypothyroidism in the present study suggests that the individual sensitivity to ¹³¹I governs the subsequent development of hypothyroidism. In the present study the risk of hypothyroidism was probably overestimated since all patients receiving levothyroxine were classified as hypothyroid although seven of 11 patients had compensated hypothyroidism. It is well accepted that this condition can be stable for several years before possible progression to manifest hypothyroidism. The risk of hypothyroidism is clearly lower than that reported for Graves' disease and not higher than that reported for nodular toxic goitre.²¹ Since the main purpose of ¹³¹I treatment is to decrease nodular volume the accompanying low incidence of hypothyroidism cannot be classified as a serious side effect. Higher ¹³¹I doses might even be contemplated. Since there is evidence of a subtle ongoing reduction in thyroidal secretion in patients remaining clinically euthyroid these patients should be offered prolonged follow up in case of possible late hypothyroidism.²²

Side effects were few and especially no clinically detectable increase in goitre size or exacerbation of obstructive symptoms were noted. The results were satisfactory, except in one patient with a small goitre (30 ml) who wished to be referred for surgery six months after treatment. Three patients developed features of hyperthyroidism one to three months after ¹³¹I therapy and needed drug treatment. The possibility of one or more of these patients having Graves' disease cannot be excluded. A similar case was described by Kay *et al.*¹⁹ Another two patients had a transient episode of radiation induced thyroiditis and mild thyrotoxicosis. Present evidence does not suggest an increased risk of thyroid malignancy or leukaemia after therapeutic doses of ¹³¹I^{23,24} and there seem to be only emotional reasons for limiting this treatment to highly selected patients.

CONCLUSION

A substantial reduction in nodular thyroid volume accompanied by a low incidence of hypothyroidism justifies the use of ¹³¹I, especially for recurrence of multinodular non-toxic goitre after surgery or in patients who may have contraindications to surgery. This treatment could be more widely used.

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Clinical implications

- The incidence of non-toxic multinodular goitre increases with age
- Some patients do not wish operation or are poor candidates for surgery
- Radioiodine is well tolerated as an outpatient procedure and can be repeated
- A 30% reduction in thyroid volume can be achieved within three months and a 50–60% reduction within 24 months
- Side effects are few and the five year risk of hypothyroidism is 22%

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Association between impaired glucose tolerance and circulating concentration of Lp(a) lipoprotein in relation to coronary heart disease

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Abstract

Objective—To examine whether impaired glucose tolerance and raised Lp(a) lipoprotein concentrations are associated in subjects with coronary artery disease.

Design—Study of two subject populations, one with and one without symptomatic coronary artery disease. Case-control analysis of patients with impaired glucose tolerance and normal glucose tolerance performed in each subject population independently.

Setting—A general practice and a hospital ward in Newcastle upon Tyne.

Subjects—517 apparently healthy subjects, 13 with impaired glucose tolerance, and 245 patients who had undergone coronary artery bypass graft surgery 12 months before, 51 with impaired glucose tolerance.

Main outcome measures—Serum Lp(a) lipoprotein concentration, plasma glucose concentration before and after oral challenge with 75 g glucose monohydrate, and Lp(a) lipoprotein isoforms.

Results—In both the asymptomatic subjects and the subjects with coronary artery disease there was no significant difference between subjects with impaired glucose tolerance and subjects with normal glucose tolerance who were matched for age, sex, and body mass index in serum Lp(a) lipoprotein concentrations (geometric mean 61 (geometric SD 4) mg/l v 83 (5) mg/l for asymptomatic subjects, 175 (3) v 197 (2) for subjects with heart disease), nor was there any difference in the proportion of subjects who had Lp(a) lipoprotein concentrations >300 mg/l (31% v 23% for asymptomatic subjects, 37% v 37%

for subjects with heart disease). For both subject groups there was no significant correlation between Lp(a) lipoprotein concentration and plasma glucose concentration after a glucose tolerance test, nor did Lp(a) lipoprotein concentration vary by quintile of glucose concentration after the test. Examination of Lp(a) lipoprotein isoforms in the subjects with coronary artery disease revealed an inverse relation between isoform size and plasma Lp(a) lipoprotein concentration, but there was no evidence that impaired glucose tolerance was associated with particular Lp(a) lipoprotein isoforms.

Conclusion—Raised Lp(a) lipoprotein concentrations are not responsible for the association between impaired glucose tolerance and coronary artery disease.

Introduction

Impaired glucose tolerance has been associated with an approximate doubling in the risk of ischaemic heart disease in studies performed in the United Kingdom.^{1,2} High circulating Lp(a) lipoprotein concentrations have also been associated with an increased risk of ischaemic heart disease.³⁻¹³ A study of people with no evidence of ischaemic heart disease suggested a fivefold increase in the prevalence of raised lipoprotein(a) concentrations (>300 mg/l) in those with impaired glucose tolerance compared with those with normal glucose tolerance.¹⁴ It was proposed that a high concentration of lipoprotein(a) may explain the increased risk of ischaemic heart disease in people with impaired glucose tolerance. To investigate this we examined the relation between glucose tolerance and circulating lipoprotein(a)