

THYROID FUNCTION AND RECURRENCE RATE FOLLOWING SURGICAL TREATMENT OF NONTOXIC GOITRE : PRELIMINARY FINDINGS

B.Bülent MENTEŞ, M.D., Erdal YILMAZ, M.D., Zafer FERAHKÖŞE, M.D.,
Bülent UÇAN, M.D., Ferruh AYOĞLU*, M.D., Ertan TATLICIOĞLU, M.D.

Gazi University, Faculty of Medicine, Departments of General Surgery and Public Health*, Ankara, Turkey

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SUMMARY

Purpose : Postoperative thyroid functions and recurrences of a selected group of our patients treated surgically for nontoxic multinodular goitre were documented and discussed from the stand point of the extent of surgery and prophylactic thyroxine. **Methods :** A total of 81 patients was grouped according to the remnant size and followed for an average of 58 months (4.8 years). **Results :** The results of our study suggest that; i) subtotal thyroidectomy is not promising for the postoperative maintenance of normal thyroid functions because about 1/3 of the patients with remnants of 6-10 g develops hypothyroidism postoperatively; ii) the unacceptably high recurrence rate after bilateral subtotal lobectomy is reduced by the postoperative administration prophylactic thyroxine; iii) the short term recurrence rate is low when bilateral near total resection is performed; iv) in spite of the normal TSH levels, patients with unilateral lobectomies have a high risk of developing nodules in the previously normal lobe, and therefore require additional preventive measures. **Conclusion :** Altogether, our results weigh in favor of performing more radical resections for nontoxic nodular goitre and utilizing the prophylactic effect of thyroxine in patients coming from endemic regions.

Key Words : Thyroid Function, Thyroid Resection, Thyroxine, Recurrence.

INTRODUCTION

Nontoxic multinodular goitre (MNG) is a common medical problem, especially in endemic regions. However, there still exists considerable debate about the extent of surgery and the efficacy of the use of postoperative prophylactic thyroxine. Unfortunately, the current literature has not yet reached a consensus on the optimum surgical treatment and a standard follow-up strategy with or without exogenous thyroxine supplementation that would provide the lowest recurrence rate and the least morbidity for patients operated on for nontoxic multinodular goitre. Some surgeons

would perform total thyroidectomy for bilateral nodular goitre or bilateral subtotal lobectomy even if one lobe is macroscopically unaffected (1, 2). This radical surgical approach is based on the common belief that a propensity toward nodular change involves the whole gland even if the initial finding is a solitary nodule at the time of operation. Others have adopted a rather conservative surgical approach and intended to spare the macroscopically normal thyroid tissue in order for at least some of their patients to maintain normal thyroid functions postoperatively (3, 4). Another important controversy is about the postoperative use of thyroxine, especially in euthyroid patients.

solely with the aim of preventing recurrence. While some studies have reported no significant differences in the recurrence rates between patients who received postoperative thyroxine and those who did not (5, 6), other studies have found postoperative thyroxine to be most efficacious (4, 7). Thus, the older rationale that multinodular goitre develops as a result of unbalanced TSH stimulation created by a biochemical block in the production of thyroxine in the thyroid gland is still debated with the more recently described autonomous nature of the disease (8). We have witnessed that such defective points in the understanding of the pathogenesis of multinodular goitre have brought about different treatment and follow-up policies in different centers, and even surgeons within the same hospital often lack a common standard practice considering the extent of surgery and/or the postoperative administration of thyroxine. Such controversies have prompted us to review the results of a selected group of our patients treated surgically for nontoxic multinodular goitre. Postoperative thyroid functions and recurrences are documented and discussed from the stand point of the extent of surgery and prophylactic thyroxine. Although the follow-up period is limited, the results might provide some preliminary data to comment on the optimum surgical strategy and the efficacy of postoperative prophylactic thyroxine, at least in this group of patients and in this region of the world.

PATIENTS AND METHODS

Patients treated surgically for colloid nodule or multinodular goitre (MNG) were reviewed. Patients with previous thyroid operations, other endocrine disorders, toxic multinodular goitre, or malignant tumors were not included in this study. None of the patients had received L-thyroxine or antithyroid drugs preoperatively. Patients with additional histopathologic diagnoses including lymphadenoid infiltration, Hashimoto's thyroiditis, or other inflammatory changes were also excluded. Therefore, the study group consisted of patients with one or more colloidal nodules, the rest of the gland being macroscopically normal. Women who became pregnant during their follow-up were also excluded from the study. The operations were carried out by the same surgical team, and the surgical policy was to resect the macroscopically pathologic thyroid tissue with clear margins. The extent of the operation depended on the site and

degree of the nodular changes. Bilateral total lobectomy was almost always performed for malignant disease, and simple enucleation, partial lobectomy, or isthmectomy were seldom performed. Thus, the surgical procedures performed for this group of patients were uniformly unilateral subtotal, near total, or total lobectomy or a combination of these procedures (plus isthmusectomy and pyramidal lobectomy) for bilateral multinodularity. The technique always included identification of the inferior laryngeal nerve and the parathyroids, and ligation and division of the superior and inferior thyroid vessels. Frequently, a sample of a cuboid volume of about 1 ml was obtained from the healthy remnant tissue and weighed in order to estimate the remnant size in grams (g). The surgical procedures were standardized to leave 3 to 5 g of thyroid tissue for a subtotal lobectomy. For near total resection, only the dorsal thyroid capsule and a thyroid tissue of about 1-2 g was left behind in order to protect the inferior laryngeal nerve and parathyroids. For bilateral procedures, the additional weight of the remnants of both sides were taken into account.

When histopathologic findings confirmed the diagnosis of colloid nodule(s), the patients were discharged without thyroxine supplementation. They were reviewed four weeks postoperatively and serum T3, T4, and TSH levels were recorded. Elevated TSH levels necessitated thyroxine supplementation (100 µg/day initially) regardless of the thyroid status. Patients with normal T3, T4, and TSH levels did not receive prophylactic thyroxine. Physical examination and thyroid function tests were repeated about six months later and then, on a yearly basis. Patients on thyroxine medication always had two controls; one while on thyroxine and the other four weeks after cessation of the drug. The dose of thyroxine was altered whenever deviation from normal T3, T4, and/or TSH levels occurred. The drug was stopped whenever euthyroidy was maintained without thyroxine supplementation and with normal TSH levels. Thyroid hypofunction was determined whenever one or both of T3 and T4 was below the lower limit together with an associated rise in TSH. During the follow-up period, any palpable thyroid tissue necessitated thyroid scintigraphy and/or ultrasonography. Nodules which arose afresh in the previously normal thyroid tissue or remnant were considered as recurrences, and in this study, they were always palpable nodules larger than 1 cm

because only patients with palpable lesions on physical examination were further evaluated by imaging techniques. Diffuse hyperplasia, confirmed by scintigraphy and/or ultrasonography, was not considered as recurrence. The follow-up period of a patient was stopped as soon as recurrence was documented. Only, patients who were followed for more than two years were included.

Serum T3, T4, and TSH levels were measured by RIA. For statistical analysis, Fisher's exact test and Chi-square test were used, and a p value of less than 0.05 was considered to represent a significant difference.

RESULTS

Among more than 400 thyroidectomies performed for nontoxic goitre between 1985 and 1993, 81 patients fulfilled the above criteria and could be followed for more than two years, postoperatively. Of the 81 patients, 12 were male and 69 were female; their age range was 18-63 years. The follow-up period averaged 58 months (4.8 years). The operative complications are beyond the scope of this article and were not discussed.

Bilateral Subtotal Lobectomy: For bilateral nodules, 45 patients underwent bilateral subtotal lobectomy (BSL), and the remnant weighed 6-10 g with a fairly symmetrical distribution on both sides. The average follow-up period was 68.2 months (5.7 years).

Four weeks after the operation 40 of the 45 patients (88 %) had elevated TSH levels, and 24 (53 %) also had subnormal T3 and/or T4 levels. One year postoperatively, 26/45 (57 %) still possessed high TSH levels, while thyroid hypofunction was noted in 13/45 (29 %). Therefore, 26 patients received thyroxine supplementation regularly during the follow-up period. Interestingly, two patients who initially possessed high TSH levels returned to an euthyroid state with normal TSH levels after three and five years, and required no medication thereafter. Within the time limits of this study, these two patients were considered to have received postoperative thyroxine supplementation.

Of the 26 patients who received postoperative thyroxine, two recurrences (8%) were noted. 19 BSL patients received either no thyroxine or only during the first 6 or 12 months postoperatively.

Seven patients in this group came for periodical controls but refused to receive thyroxine although they had elevated TSH levels and one of them developed symptoms of hypothyroidism, also confirmed biochemically. These seven patients were either reluctant to take the drug or they blamed thyroxine for symptoms such as headache, palpitation, or diarrhea. Overall, the group of 19 patients who received no thyroxine developed six recurrences (32 %). Three of the six recurrences occurred in the group of seven patients without thyroxine and with high TSH levels. Of the 12 patients without thyroxine but with normal TSH values, three additional recurrences were noted.

Thus, a total of eight recurrences occurred in the two BSL groups. The recurrence rate of the group of patients who did not receive postoperative thyroxine was higher than that of the thyroxine group with a marginal significance ($p=0.0545$), although the two groups did not differ with respect to the mean age or the mean follow-up period.

Near Total Thyroidectomy: Ten MNG patients underwent bilateral near total lobectomy. The reason for the more extensive resection was the position and the number of nodules. These patients were followed for an average of 43.6 months (3.6 years), All of the patients were female.

Four weeks after the operation, nine of the ten patients (90%) had elevated TSH. Seven patients (70 %) also had subnormal T3 and/or T4 levels. Interestingly, one patient (10 %) maintained an euthyroid state with normal TSH, as soon as four weeks after the operation. The biochemical pattern of all ten patients remained the same during the follow-up period. Therefore, 9/10 patients received regular thyroxine supplementation postoperatively. During the follow-up period, no recurrences were recorded in this group.

Unilateral Lobectomy: For nodules confined to a single lobe, 26 patients underwent unilateral procedures consisting of total, near total, or subtotal lobectomies. Thus, at least one thyroid lobe was left behind, indicating a remnant size of 12-20 g. The patients were followed for an average of 47.3 months (3.9 years).

Four weeks after the operation, only four of the 26 patients (15%) had elevated TSH levels, and only one of them (4%) also had a low T3 level. One year postoperatively, 3/26 patients still had high TSH but normal T3 and T4 levels (12%). One

patient (4%) developed permanent hypothyroidism. Thus only 4 patients (15 %) required postoperative thyroxine, while 22 patients (85 %) were not supplemented.

Of the 26 patients with unilateral lobectomies, six recurrences developed, indicating an overall recurrence rate of 23%, within the time limits of this study. Five recurrent cases had nodule(s) within the nonoperated lobe, while one patient with subtotal lobectomy developed nodules both in the virgin lobe and on the operated side. None of the patients who developed recurrent nodules had received postoperative thyroxine. Therefore, if we disregard the four patients who received thyroxine supplementation, six out of 22 patients turned out to have developed recurrences, and the ratio increased to 27 %.

DISCUSSION

The main objective of surgical treatment of nontoxic multinodular goitre is to remove the pathologic thyroid tissue and to confirm the absence of malignancy, histopathologically. Multinodular goitre is an endemic event in the Anatolian region of Turkey, mainly due to iodine deficiency. Patients with this disease entity constitute a considerable proportion of the patients operated on at our surgical department. Growing solid nodules larger than 1 cm in diameter, resistance to thyroxine therapy, recurrent cystic nodules, inability to rule out malignancy, local compression symptoms, and/or cosmesis were the major indications for surgical intervention. Although the indications for surgical treatment are still controversial, this point is beyond the aim of this study. Nevertheless, our pathology department reports that only 3 % of the recently resected thyroid specimens turned out to contain malignant foci. In this setting, most of the surgeons are prone to resect only the affected lobe or the macroscopically pathologic thyroid tissue and leave behind as much normal remnant as possible. The rationale is that at least some of their patients might maintain an euthyroid state postoperatively. Although such an approach may appear promising in eliminating the need for long-term, expensive and burdensome thyroxine medication, factors that determine postoperative functions and recurrence rates are yet controversial. Besides, the time course of the new steady state of the hypothalamus-pituitary-thyroid axis is not well-defined. To add more to the difficulty, the prophylactic effect of

postoperative thyroxine administration in patients with normal thyroid hormone levels is still debated.

Postoperative Thyroid Functions :

In this study, patient selection criteria were carefully standardized in order to exclude the possible factors other than the remnant size, such as any inflammatory or malignant changes, preoperative thyroxine administration, or interfering pregnancy, which might influence postoperative thyroid functions. In this setting, the remnant size appeared to be one of the major factors that influenced postoperative hormone levels. When the remnant weighed more than 12 g, such as in unilateral lobectomies, 96% of the patients was euthyroid and 85% also possessed normal TSH levels, one year after surgery. When the remnant size was reduced to 6-10 g (BSL), euthyroidy was maintained in 71% and normal TSH levels in 43%. Smaller remnants rendered only 30% of the patients euthyroid, and only 10% had normal TSH levels. Also important to note is the fact that the number of patients with high TSH and/or low thyroid hormone levels four weeks postoperatively decreased one year after surgery. Two patients in the BSL group returned to euthyroid state with normal TSH levels three and five years after surgery. Thus, the new steady state appears to develop fully many months or even years after surgery. The dynamic postoperative restitution of thyroid function is TSH-dependent, and an initial postoperative rise of TSH may be followed by normalization (9). In another study, this restitution period was reported to take about 18 months after thyroidectomy (5). Serum T3 levels are also known to fall in association with surgical trauma, but after a few days rise again to outset values (10). Bearing these facts in mind, it is logical to decide about the thyroid status at least one year after the operation.

Various previous studies of thyroid function after thyroidectomy have also indicated a direct relationship between the incidence of hypothyroidism and the remnant size in nontoxic patients. Young and MacLeod expressed an optimum remnant as being 8 ml (11). Griffiths and coworkers suggested that 20% of the nontoxic patients with remnants of less than 6 ml became hypothyroid and 47% had elevated TSH levels, while none of the nontoxic patients with remnants of between 6-16 ml developed hypothyroidism but TSH levels were elevated in 27%, one year after surgery (12). Geerdson and Frolund reported that

thyroid function and TSH levels returned to baseline values within 18 months of postoperative observation in all of their patients, including 10 who had undergone BSL, although the remnant sizes were not recorded (5). These findings suggested that factors other than the remnant size, such as the patient's age, surgical technique, environmental, or even racial factors might influence postoperative thyroid functions. Lymphadenoid infiltration of the thyroid, for example, has been discussed as a possible factor which might influence postoperative thyroid functions (12). We will suffice to say that the study group was free of any diffuse thyroid disorders and preoperative TSH suppression. Further studies including multivariate analyses of carefully documented cases are necessary to define these factors.

In spite of the careful selection of the patient groups, we cannot explain why some of the patients developed hypothyroidism while some others with the same remnant size maintained normal functions. Nevertheless, postoperative thyroid hypofunction was frequent in our group of patients coming from an iodine-deficient region unless at least one lobe was left untouched. Unlike the above cited results obtained in iodine-rich areas, about 1/3 of our patients who had undergone BSL developed hypothyroidism. Although the correlation between the remnant size and thyroid hormone levels still exists, our results suggest that subtotal thyroidectomy does not yield satisfactory results regarding the maintenance of postoperative normal thyroid functions. This fact might apply to the population groups from other iodine-deficient regions of the world.

Recurrence of Goitre with Respect to the Extent of Thyroidectomy and Prophylactic Thyroxine :

The reported incidence of nodular recurrence following subtotal thyroidectomy for MNG ranges from uncommon (4, 13) to as high as 45 %, most of the recurrences occurring many years after surgery (8, 14). Owing to the unsuccessful long term results, considerable debate about the optimum surgical management of nontoxic goitre still exists. Different treatment policies, which are based on individual observations and concerns but not on concrete scientific data, largely result from an incomplete understanding of the pathogenesis of MNG. Some authors advocate meticulous selection of only the pathologic tissue and report good results

with conservative surgical treatment, especially if surgery is followed by simple prophylaxis with thyroxine (3, 4). This strategy is based on the postulation that a single or a few progeny cell lines with somatic mutations and preferential growth advantages cause nodule formation and this pathologic process is promoted by long-standing stimulation by TSH (8). Thus, conservative surgery with removal of the neoplastic tissue and postoperative TSH suppression are considered adequate. Other authors have suggested more radical surgical treatment to prevent recurrences. They performed BSL even if one lobe was macroscopically normal at the time of operation or total thyroidectomy for bilateral nodular glands with excellent results (1, 2). This radical approach is based on the belief that the pathologic process or at least a propensity toward multinodular change involves the whole gland. Although the initial pathologic process may appear as a solitary nodule or a number of nodules, it is likely that, in time, the condition will become generalized. Therefore, extensive resection of the thyroid reduces the possibility of future nodular recurrence, whatever the promoting factors are.

The use of thyroxine in the postoperative prophylaxis of MNG is another important controversy that deserves discussion. There is a wealth of conflicting reports in the literature substantiating both sides of the argument. Although thyroid hormone therapy is often used after thyroidectomy, the physiopathologic basis of its prescription is disputable. In a five-year follow-up study of 266 patients, it was found that 86 patients who received regular thyroxine prophylaxis had no recurrences, while 17 recurrences (9.4 %) developed in the group of 180 patients who did not take thyroxine (15). Anderson and coworkers supported the efficacy of prophylactic postoperative thyroxine and reported a significant reduction of nodular recurrence (5.3 %) in 171 patients who were observed for a mean period of 10.25 years (4). When recurrences did occur in the thyroxine treated group, they were small and were easily managed by increasing the dose of thyroxine. A sonographic follow-up study of 104 patients from a region with low iodine intake reported a relative reduction in the thyroid volume and a significantly lower recurrence rate in patients who received prophylactic postoperative thyroxine, compared with those who did not (7) On the contrary, no significant difference in the

recurrence rate between the patients who took thyroxine and those who did not was noted in another study of 175 patients followed for 8.8 years postoperatively (16). Rojdmarm and Jarhuld suggested that long term oral thyroxine did not influence the high long term recurrence rates after subtotal thyroidectomy for nodular goitre (14). Kraimps and coworkers suggested that postoperative hormone therapy may have delayed but did not prevent recurrent MNG, and once postoperative nodule recurrence was documented, thyroxine treatment did not inhibit further growth (13). Although some investigations have documented that the subsets of follicular cells which cause nodular dysplasia may replicate even in the absence of TSH (17,18), the additive promoting role of TSH still exists. Consequently, thyroid hormone may still be used in an attempt to reverse or prevent thyroid growth by suppressing TSH's direct thyrotrophic effect and any permissive effect on other growth factors such as epidermal growth factor (17).

We believe that the inconsistency of the above cited results of some treatment strategies results, to some extent, from the inability to differentiate racial and/or environmental factors, namely iodine intake. Randomized studies should be conducted on individual population groups and the results should apply specifically to these groups of patients. This study provided preliminary data that might mediate future operative strategies and postoperative prophylactic measures, as far as the white population from iodine deficient regions is concerned. The recurrence rates were unacceptably high in the BSL group, especially in those who did not receive postoperative thyroxine, and in patients who had undergone unilateral lobectomy. Besides, the patients were further evaluated only if palpable lesions were identified on physical examination, suggesting the possibility that the recurrence rates might actually be much higher. Recurrence is also a function of time, and more recurrences may be expected to appear after five or ten years (8). The recurrence rate was lower in BSL patients who received postoperative thyroxine, compared with that of the BSL patients who did not take the drug. This difference almost reached significance within an observation period of five years ($p=0.0545$). This finding is in accordance with the previous report of Kzepka et al. who identified patients from iodine-deficient areas (7). This reported success of hormone suppression therapy, as well as ours, in

preventing nodular recurrence may also be related to the iodine status within the population studied, because failure of levothyroxine to significantly reduce the volume of MNG is common in countries where iodine supplementation has almost eradicated endemic goitre while hormone suppression therapy is relatively successful in endemic countries (19). Of the seven patients in the BSL group who did not receive thyroxine and who also had high TSH levels, three recurrences developed. Although the number of patients in this category are too small to build up a statistical analysis, this high recurrence rate supports the possible promoting effect of TSH in recurrence. We cannot comment on the specific levels of TSH which might provide a better suppression because we only intended to keep TSH levels below the upper limit. Therefore, our results suggest that prophylactic thyroxine should be prescribed to patients after BSL, regardless of the thyroid functions.

None of the patients who underwent near total thyroidectomy developed recurrence during the average observation period of 3.6 years. Although the number of patients in this group was also small and the follow-up period was short, this finding is suggestive. The smaller remnant size appears to reduce the risk of nodular recurrence (8). In experienced hands, complications of a more extensive thyroid resection should not be different or more frequent from those of BSL. As stated above, about 1/3 of our patients developed hypothyroidism after BSL. Therefore, leaving a total of 6-10 g remnant on both sides does not result in normal postoperative functions in a considerable number of patients, and even euthyroid BSL patients are to receive prophylactic thyroxine, anyway. Although the BSL group and the near total thyroidectomy group were not comparable with respect to the number of patients, sex distribution, and the follow-up period, a total or near total thyroidectomy appears to be an attractive surgical alternative to BSL in our patients. To our belief, prophylactic thyroxine should be given postoperatively to all patients in this group without further evaluation, although one of our patients (10%) maintained euthyroid status with normal TSH levels.

Of the 22 patients who had undergone unilateral lobectomies and maintained euthyroid status, the recurrence rate was 23% within the time limits of

this study, although TSH levels were also within normal limits. A unilateral procedure and the lack of need for postoperative controls and medications may initially appear easy and comfortable both for the patient and the surgeon. On the other hand, such an approach resulted in a high recurrence rate in our patients, most of the nodules developing in the previously untouched lobe. We unfortunately lack other study groups to comment on the possible effects of postoperative prophylactic thyroxine or the results of a more extensive surgical approach. Still, the high recurrence rate suggests that a more extensive resection involving the initially normal lobe is a serious alternative, as suggested by many authors. Prophylactic thyroxine should be considered in patients who previously underwent a unilateral procedure because this is yet the only available prophylactic agent.

In conclusion, further controlled studies are necessary in order to achieve the best long term results with the least morbidity in patients with nontoxic nodular goitre. Our results might provide some preliminary data to comment on the defective points of the surgical interventions and the efficacy of postoperative prophylactic thyroxine, at least in this group of patients and in this region of the world. A conservative surgical policy without postoperative thyroxine prophylaxis results in considerably high numbers of early recurrence even with normal TSH levels. The results of our study suggest that; i) subtotal thyroidectomy is not promising for the postoperative maintenance of normal thyroid functions because about 1/3 of the patients with remnants of 6-10 g develops hypothyroidism postoperatively; ii) the unacceptably high recurrence rate after bilateral subtotal lobectomy is reduced by the postoperative administration prophylactic thyroxine; iii) the short term recurrence rate is low when bilateral near total resection is performed; iv) in spite of the normal TSH levels, patients with unilateral lobectomies have a high risk of developing nodules in the previously normal lobe, and therefore require additional preventive measures. Altogether, our results weigh in favor of performing more radical resections for nontoxic nodular goitre and utilizing the prophylactic effect of thyroxine in patients coming from endemic regions.

Correspondence to : Dr.B.Bülent MENTEŞ
Gazi Üniversitesi Tıp Fakültesi
Genel Cerrahi Anabilim Dalı
06500 ANKARA - TÜRKİYE
Phone : 312 - 214 10 00 / 5747
Fax : 312 - 222 66 37

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