

## CLINICAL STUDY

# Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine

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## Abstract

**Objective:** To investigate the long-term effects of continuous methimazole (MMI) therapy.

**Design and methods:** Five hundred and four patients over 40 years of age with diffuse toxic goiter were treated with MMI for 18 months. Within one year after discontinuation of MMI, hyperthyroidism recurred in 104 patients. They were randomized into 2 groups for continuous antithyroid and radioiodine treatment. Numbers of occurrences of thyroid dysfunction and total costs of management were assessed during 10 years of follow-up. At the end of the study, 26 patients were still on continuous MMI (group 1), and of 41 radioiodine-treated patients (group 2), 16 were euthyroid and 25 became hypothyroid. Serum thyroid and lipid profiles, bone mineral density, and echocardiography data were obtained.

**Results:** There was no significant difference in age, sex, duration of symptoms and thyroid function between the two groups. No serious complications occurred in any of the patients. The cost of treatment was lower in group 1 than in group 2. At the end of 10 years, goiter rate was greater and antithyroid peroxidase antibody concentration was higher in group 1 than in group 2. Serum cholesterol and low density lipoprotein-cholesterol concentrations were increased in group 2 as compared with group 1; relative risks were 1.8 (1.12–2.95,  $P < 0.02$ ) and 1.6 (1.09–2.34,  $P < 0.02$ ) respectively. Bone mineral density and echocardiographic measurements were not different between the two groups.

**Conclusion:** Long-term continuous treatment of hyperthyroidism with MMI is safe. The complications and the expense of the treatment do not exceed those of radioactive iodine therapy.

*European Journal of Endocrinology* 152 695–701

## Introduction

The major clinical problem of antithyroid therapy is the 20–70% relapse of hyperthyroidism following discontinuation of treatment (1–5). Reports of low remission rate therapy (6, 7) and ease, effectiveness and low expense of radioiodine therapy (8, 9), has led to increasing reliance on radioiodine treatment for hyperthyroidism. In fact, more than two thirds of the members of the American Thyroid Association choose radioiodine as the treatment of choice for virtually all patients with Graves' disease (10). This practice is not common in members of the European Thyroid Association, since two thirds of these prefer antithyroid drugs as the first approach to the treatment of hyperthyroidism (11). However, almost all thyroidologists agree that the treatment of choice in cases of recurrence after original therapy is that of radioiodine.

Hypothyroidism occurs in 50–70% of patients after low dose and in 90–100% following high dose radioiodine treatment (12, 13). Over replacement of thyroxine may cause alterations in heart (14, 15) and bones

(16, 17) and the potency, uniformity and reproducibility of thyroxine preparations may be variable (18, 19). Adding these to the lack of patients' compliance (20, 21) may make the long-term precise management of hypothyroidism somewhat problematic.

The aim of this study was to investigate the effectiveness of continuous antithyroid drug treatment and to compare the benefits and side effects of the said therapy with those of radioiodine treatment.

## Materials and methods

This randomized controlled clinical trial was performed between March 1989 and June 2002 in Tehran, Iran.

### Selection of patients

Patients older than 40 years of age, diagnosed with hyperthyroidism due to diffuse toxic goiter were treated with methimazole (MMI); five hundred and four patients were enrolled for the study. Patients were kept euthyroid by MMI therapy, and at the end

of 18 months of treatment, MMI was discontinued. Twelve patients had a relapse of disease while on treatment, 21 were lost at follow-up and eight chose ablation therapy. These 41 patients (8%) were excluded from the study.

Within one year after discontinuation of MMI therapy, 104 of 463 patients (22%) experienced overt symptoms and signs of hyperthyroidism. They were assigned by randomization into two groups for treatment with either MMI or radioactive iodine, adopting random sampling numbers. Nineteen patients wanted treatment options other than those offered by random allocation and were excluded from the study. Eventually, 34 patients in the MMI group and 51 patients in the radioiodine group remained for additional study.

### Study protocol

Thirty-four patients received 10 mg MMI twice daily during the first month and 10 mg daily during the second month of therapy. All patients received maintenance doses of 2.5–10 mg daily from the third month on; MMI administration continued and 26 patients (78%) completed 10.2±0.5 years of follow-up (range 9.2–11.1 years).

Radioiodine was delivered to 51 patients in doses calculated using the following formula:

$$\text{Dose} = \frac{(100 \mu\text{Ci } ^{131}\text{I/g thyroid}) \times \text{thyroid weight (g)}}{23\text{-h radioiodine uptake}}$$

The mean dose of radioiodine was 7.9±5.1 mCi with a range of 5 to 13 mCi. Forty-one patients (80%) returned for follow-up visits for 10.1±0.4 years (range 9.3–10.9 years).

After monthly visits for the first 3 months of therapy, all patients in both groups were visited every 3 months for the first year and, if stable, every 6 months thereafter. At each visit, a complete history was taken, a physical examination was performed and the side effects of treatment were ascertained. A blood sample for cell blood count (CBC) and the measurement of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), thyroxine (T<sub>4</sub>), tri-iodothyronine (T<sub>3</sub>), free (f) T<sub>4</sub>, free (f) T<sub>3</sub> and thyrotropin (TSH) concentrations were obtained from each patient. Numbers of occurrences of thyroid dysfunction during the years of follow-up were recorded. Diagnoses of hyper- or hypothyroidism both overt and subclinical were made according to the following criteria: euthyroid (TSH level within the normal range, 0.1–5.0 mU/l inclusive); hypothyroid (TSH > 5.0 mU/l and T<sub>4</sub> < 4.5 µg/dl); subclinical hypothyroid (TSH > 5.0 mU/l, T<sub>4</sub> ≥ 4.5 µg/dl, fT<sub>4</sub> ≥ 0.7 ng/dl); hyperthyroid (TSH < 0.1 mU/l, T<sub>4</sub> > 12.5 µg/dl and/or T<sub>3</sub> > 200 ng/dl) and subclinical hyperthyroid (TSH < 0.1 mU/l, T<sub>4</sub> ≤ 12.5 µg/dl, fT<sub>4</sub> ≤ 2.0 ng/dl and T<sub>3</sub> ≤ 200 ng/dl). In all patients the dosage of MMI or L-thyroxine was adjusted to maintain

patients in a euthyroid state and to keep serum T<sub>4</sub> and T<sub>3</sub> concentrations within the middle range of normal values.

**Final visit** At the end of the study, weight and height were measured and body mass index (BMI) was calculated. A questionnaire was completed to assess the status of cigarette smoking and the history of age at menarche and menopause in women. A research dietitian using dietary recall estimated the level of calcium intake. Physical activity was assessed by the Lipid Research Clinic questionnaire (22) and the quality of life was evaluated by a specific questionnaire SF-36 (23). A thorough physical examination was performed and goiter was graded according to the World Health Organisation (WHO) classification (24). The same doctor (L A) carried out all assessments of goiter by palpation. Every patient had a lipid profile, and measurements of calcium, phosphorus, parathyroid hormone (PTH), thyroid function tests and thyroid antibodies, 24-h urine-free deoxyypyridinoline, bone mineral density, electrocardiography (EKG) and echocardiography were performed.

The Human Research Review Committee of the Shaheed Beheshti University of Medical Sciences approved the study, and informed consent was obtained from all patients.

### Measurement and procedures

Serum ALT, AST, bilirubin, alkaline phosphatase, creatinine, calcium, phosphorus cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C) measurements were carried out using routine methods and low-density lipoprotein cholesterol (LDL-C) was calculated. Excretion of free deoxyypyridinoline in 24-h urine samples was measured by radioimmunoassay using a Gamma BCT DPD kit from Immunodiagnostic Systems Limited, Boldon, UK.

**Hormone and antibody measurements** Serum T<sub>4</sub> and T<sub>3</sub> were measured by radioimmunoassay, and serum TSH by immunoradiometric assay using kits from Orion Diagnostica (Espoo, Finland). We measured fT<sub>4</sub> and fT<sub>3</sub> by saturation analysis using kits from Diagnostic Products Co. (Los Angeles, CA, USA) intact PTH by the ELISA method using kits from Diagnostic Systems Laboratories, Inc. (Webster, TX, USA), antithyroperoxidase antibody (TPOAb) and antithyroglobulin antibody (TgAb) by immunoenzymometric assay (Radim, Pomezia, Rome, Italy) and urinary iodine levels by a digestion method (24).

Reference ranges of serum parameters for euthyroid adult subjects are: T<sub>4</sub>, 4.5–12.5 µg/dl; T<sub>3</sub>, 80–200 ng/dl; TSH, 0.1–5.0 mU/l (µU/ml); fT<sub>4</sub>, 0.7–2.0 ng/dl; fT<sub>3</sub>, 2.2–5.0 pg/ml; PTH, 8.8–76.6 pg/ml; TPOAb, < 100 IU/ml; TgAb, < 100 IU/ml. To convert values to SI units, for T<sub>4</sub>, T<sub>3</sub> and PTH

multiply by 12.87, 0.01536 and 0.80 respectively. Interassay and intra-assay coefficient of variations for all tests were less than 8 and 10% respectively.

**Bone mineral density** Bone mineral density (BMD) was measured by dual-energy-X-ray absorptiometry (DEXA) with a Lunar DPX device (Madison, Wisconsin, USA). Densitometry was performed on L1–L4 vertebral regions, femur (neck, trochanter, ward and total) and forearm (mid shaft, upper distal part and total radius). BMD was expressed in units as gram per square centimeter and as Z scores. The Z score was calculated as the number of standard deviations between the patients' BMD and the age- and sex-matched reference mean value. Precision errors, established with a local normal population, were less than 1.46% for all locations (spine, hip and radius).

**Echocardiographic and Doppler measurements** Complete M-mode and two-dimensional Doppler echocardiographic analysis was performed with an ultrasound mechanical system equipped with a 3.5 MHz transducer (Kontron Instruments Sigma 44 hvcd). M-mode and two-dimensional recordings were obtained with the patients in the lateral recumbent position.

### Costs

Costs were calculated from the actual expenses incurred during nearly 10 years of follow-up in each of the two groups. Hospital and ambulatory costs for thyroid-related events and illnesses were calculated and added to the total costs for each patient in the three groups. All costs were actual and when obscure (less than 15%), were estimated from the perspectives of the health care system. They are expressed both in Iranian rials and US dollars.

### Statistical analysis

We planned to enroll 102 patients for the study before randomization. This sample estimate was based on data from the literature that up to 50% of hypothyroid patients on levothyroxine are non compliant and may have increased serum TSH (20, 21), and that nearly 5–20% of hyperthyroid patients treated with MMI for 1–2 years may eventually develop thyroid failure (2, 7). To detect an absolute difference in number of events with increased TSH in group 1 and those patients in group 2 who developed hypothyroidism, with two sided alpha level  $<0.05$  and a power of 0.90, the number in each group was estimated to be 25. Since nearly 40–50% of radioiodine-treated patients may not develop thyroid failure (6–9) and considering the 35% attrition rate, we planned to have 51 patients in each of the radioiodine- and MMI-treated groups. Base-line and outcome variables were compared with the use of Student's *t*-test, Mann-Whitney, chi-square and Fisher's exact tests. To determine relative risk, the percent of goiter, the number of patients with reduced bone mineral density below 1.5 S.D. of Z scores and the number of patients with serum cholesterol above 200 mg/dl and LDL-C over 130 mg/dl in both groups of MMI-treated and radioiodine-treated hypothyroid patients were considered. A value of  $P < 0.05$  was considered significant. Statistical analysis was performed using SPSS 9.05 software (SPSS Inc., Chicago, IL, USA).

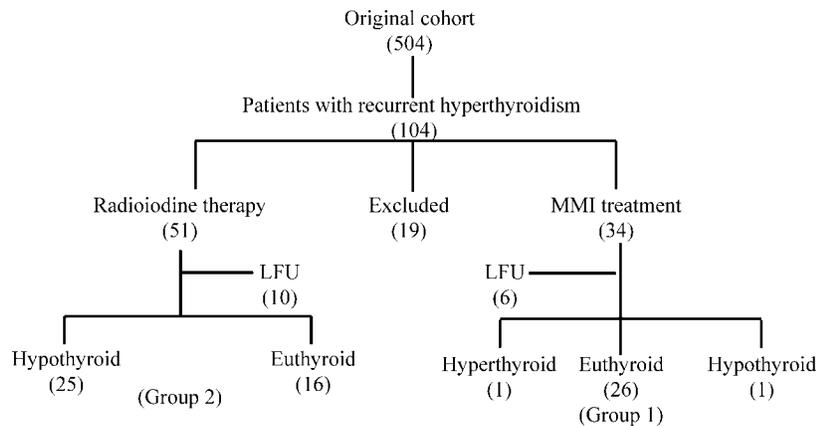
### Results

No statistical differences in age, sex, duration of symptoms, size of goiter and thyroid function tests were seen in the patients in the MMI-treated or radioiodine-treated groups at the time of randomization, before treatment or in those patients who were excluded from the study (Table 1).

**Table 1** Baseline characteristics of 104 patients with recurrent hyperthyroidism before treatment with MMI or radioiodine. Results are means  $\pm$  S.D.

Parameter	Group		
	MMI ( <i>n</i> = 34)	Radioiodine ( <i>n</i> = 51)	Excluded ( <i>n</i> = 19)
Age (years)	47 $\pm$ 5	48 $\pm$ 6	47 $\pm$ 6
Sex (F/M)	28/6	41/10	16/3
Duration of symptoms (days)	21 $\pm$ 7	19 $\pm$ 8	22 $\pm$ 9
Estimated thyroid weight (g)	36 $\pm$ 7	35 $\pm$ 8	37 $\pm$ 8
Serum T <sub>4</sub> ( $\mu$ g/dl)	18.8 $\pm$ 4.0	19.9 $\pm$ 4.7	19.7 $\pm$ 4.9
Serum T <sub>3</sub> (ng/dl)	560 $\pm$ 58	521 $\pm$ 46	547 $\pm$ 52
Free T <sub>4</sub> (ng/dl)	3.04 $\pm$ 0.87	3.12 $\pm$ 0.96	3.07 $\pm$ 1.02
Free T <sub>3</sub> (pg/ml)	11.5 $\pm$ 1.3	10.4 $\pm$ 1.0	10.4 $\pm$ 1.2
Serum TSH (mU/l or $\mu$ U/ml)	0.012 $\pm$ 0.001	0.014 $\pm$ 0.001	0.013 $\pm$ 0.001
Positive antithyropoxidase (%)	68	66	70
Positive antithyroglobulin (%)	54	51	52

To convert values to SI units for T<sub>4</sub> and T<sub>3</sub> multiply by 12.87 and 0.01536 respectively.



LFU: Lost follow up

**Figure 1** The occurrence of eu-, hyper- and hypothyroidism in 104 patients with recurrent hyperthyroidism who were randomly assigned to MMI or radioiodine therapy. Numbers in parantheses indicate number of patients in each group.

### Final thyroid status

Final thyroid status in 84 patients who completed 9.3–11.1 years of follow-up is shown in Fig. 1. Of 34 patients who were treated with MMI, 26 patients (78%) completed a mean of 10.2 years of follow-up (group 1). Mean  $\pm$  S.D. daily dosage of MMI was  $4.9 \pm 1.3$  mg in this group.

Forty-one patients in the radioiodine group completed a mean of 10.1 years of follow-up (group 2) and 10 patients were lost at follow-up. Nine patients required 1 to 3 additional doses of radioiodine and 6 out of 9 became hypothyroid. Ultimately, 16 patients (39%) remained euthyroid and 25 patients (61%) became hypothyroid 3 months to 8 years after receiving radioiodine treatment.

### Events and costs during follow-up

During 10 years of successive MMI treatment in the 26 patients of group 1, except for minor allergic symptoms, no serious complications, including agranulocytosis, occurred. Patients in group 1 had 627 measurements of thyroid function tests with 37 of these (5.9%) showing a TSH level of more than 5.0 mU/l and 48 (7.6%) showing a TSH level below 0.3 mU/l. In patients of group 2, 989 measurements of thyroid function tests were carried out. On 127 occasions (12.8%), TSH was over 5.0 mU/l and on 90 occasions (9.1%) it was below 0.3 mU/l. Corresponding figures were 21.1% and 14.9% in 25 patients who became hypothyroid after radioiodine therapy ( $P < 0.001$  and  $< 0.01$ , as compared with group 1 respectively).

The overall costs of management of hyperthyroidism and related complications was  $5070000 \pm 26000$  rials ( $\$631 \pm 32$ ), and  $5530000 \pm 29000$  ( $\$691 \pm 36$ ) in groups 1 and 2 respectively ( $P < 0.001$ ).

### Variables at the final visit

The clinical and biochemical data in 67 patients at the end of the study are summarized in Table 2. At the final visit, 2 patients in group 1 and 3 patients in group 2 were still menstruating, and the rest of the female patients were in menopause. In addition, there were

**Table 2** Clinical and biochemical variables at the end of the study in the two groups of patients with hyperthyroidism. Values are means  $\pm$  S.D.

Variable	Group 1 (n = 26)	Group 2 (n = 41)
<b>Clinical variables</b>		
Age (years)	57 $\pm$ 6	59 $\pm$ 7
Body mass index (kg/m <sup>2</sup> )	28.1 $\pm$ 4.1	28.5 $\pm$ 3.9
Current smoking (% of patients)	29	15
Daily consumption of calcium (g)	595 $\pm$ 268	484 $\pm$ 264
Systolic blood pressure (mmHg)	130 $\pm$ 21	136 $\pm$ 18
Diastolic blood pressure (mmHg)	81 $\pm$ 12	79 $\pm$ 11
Pulse rate (n/min)	81 $\pm$ 12	78 $\pm$ 13
Total goiter rate (%)	50	25†
<b>Biochemical variables</b>		
Serum T <sub>4</sub> ( $\mu$ g/dl)	9.6 $\pm$ 2.4	9.3 $\pm$ 2.8
Serum T <sub>3</sub> (ng/dl)	179 $\pm$ 34	167 $\pm$ 28
Serum free T <sub>4</sub> (ng/dl)	1.55 $\pm$ 0.50	1.63 $\pm$ 0.44
Serum free T <sub>3</sub> (pg/ml)	3.66 $\pm$ 0.72	3.44 $\pm$ 0.77
Serum TSH (mU/l)	1.7 $\pm$ 1.7	4.3 $\pm$ 6.4
Antithyroperoxidase antibody (IU/ml)	244 $\pm$ 277	45 $\pm$ 81†
Antithyroglobulin antibody (IU/ml)	293 $\pm$ 138	244 $\pm$ 266
Cholesterol (mg/dl)	190 $\pm$ 47	224 $\pm$ 46‡
Triglycerides (mg/dl)	158 $\pm$ 81	164 $\pm$ 65
LDL-cholesterol (mg/dl)	99 $\pm$ 41	132 $\pm$ 46‡
HDL-cholesterol (mg/dl)	58 $\pm$ 14	59 $\pm$ 13
Serum creatinine (mg/dl)	1.00 $\pm$ 0.23	0.99 $\pm$ 0.21
Serum calcium (mg/dl)	9.03 $\pm$ 0.46	9.10 $\pm$ 0.58
Serum phosphorus (mg/dl)	3.99 $\pm$ 0.51	4.15 $\pm$ 0.54
Serum PTH (nmol/l)	42 $\pm$ 40	44 $\pm$ 33

To convert values to SI units: for cholesterol, triglycerides, T<sub>4</sub> and T<sub>3</sub> multiply by 0.02586, 0.01129, 12.87 and 0.01536 respectively.

† $P < 0.05$ , ‡ $P < 0.01$ , compared with group 1.

no significant differences in age of menarche and start and duration of menopause in women, physical activity, CBC, blood indices, and serum concentrations of alkaline phosphatase, ALT, AST and bilirubin between the two groups.

Before randomization, goiter was present in 79.2% of the cases. At the end of the study, the total goiter rate was 50% in group 1 and 25% in group 2 ( $P < 0.05$ ). Mean serum concentrations of  $T_4$ ,  $T_3$ ,  $fT_4$ ,  $fT_3$ , and TSH concentrations were not significantly different between the two groups (Table 2). Mean TPOAb titer was significantly higher in group 1 as compared with group 2. The frequency of TPOAb above 100 IU/ml was 52% and 16% in groups 1 and 2 respectively ( $P < 0.01$ ).

Serum cholesterol and LDL-cholesterol concentrations were significantly increased in group 2 as compared with group 1 ( $P < 0.01$ ). The frequency of cholesterol above 200 mg/dl (5.17 mmol/l) was 35% and 74% and that of LDL-cholesterol above 130 mg/dl (3.36 mmol/l) was 22% and 52.6% in groups 1 and 2 respectively.

At the end of the study, the mean Z scores for BMD were lower, but not significantly so, in group 2 in all locations, as compared with group 1 (Table 3). Urinary concentration of free deoxyypyridinoline was  $21.2 \pm 14.1$  and  $30.1 \pm 27.3$  mmol/mmol creatinine in groups 1 and 2 respectively (not statistically significant, NS).

There were no significant changes in echocardiographic data between the two groups. Mean scores of the questionnaires for quality of life were  $41 \pm 9.5$  and  $40 \pm 10$  (NS) for mental and  $48 \pm 9$  and  $46 \pm 7$  (NS) for physical components in groups 1 and 2 respectively.

When relative risks of variables were compared between the two groups, a significant reduction in numbers of patients with suppressed serum TSH levels during follow-up and in the percentage of patients with hypercholesterolemia and elevated LDL-cholesterol were found in group 1 (Fig. 2). Meanwhile, the relative risk for total goiter rate and elevated antithyropoxidase favored radioiodine treatment.

**Table 3** Bone mineral density at the end of the study. Results are means  $\pm$  S.D. of Z scores.

Variable	Group 1 (n = 26)	Group 2 (n = 41)
Hip		
Total	$-0.31 \pm 0.84$	$-0.54 \pm 0.94$
Neck	$-0.22 \pm 0.72$	$-0.55 \pm 0.95$
Trochanter	$-0.36 \pm 0.88$	$-0.67 \pm 1.01$
Radius		
Total	$-1.41 \pm 1.20$	$-1.70 \pm 1.11$
Distal	$-1.10 \pm 1.24$	$-1.48 \pm 1.11$
Midshaft	$-1.33 \pm 0.98$	$-1.55 \pm 1.02$
Vertebra (L2-L4)	$-0.09 \pm 1.27$	$-0.26 \pm 1.20$

## Discussion

In the present study, we focused on the potential benefit of long-term continuous methimazole therapy for diffuse toxic goiter. Nearly 10 years of follow-up of such patients showed that this mode of treatment is safe and its cost does not exceed that of radioiodine treatment.

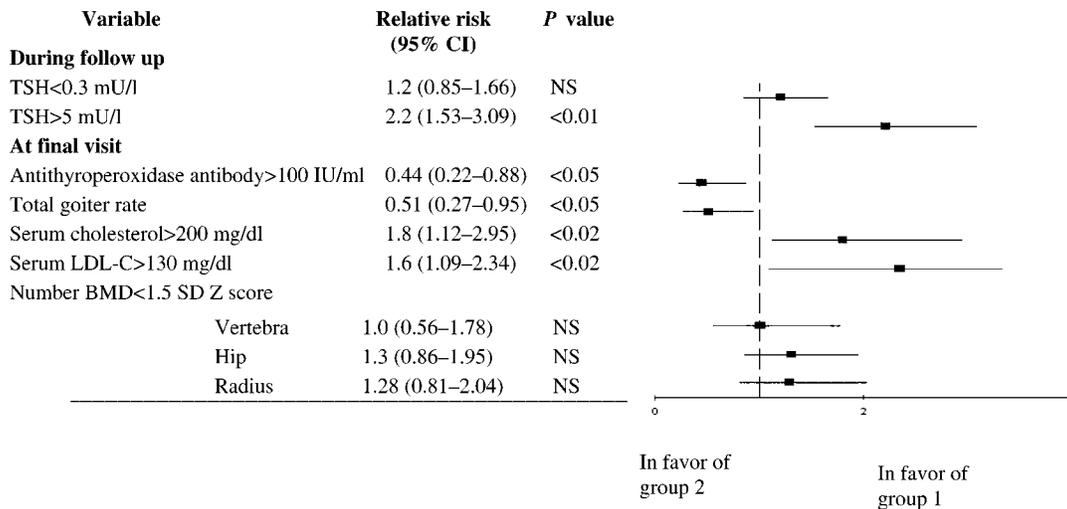
The most obvious objective in the treatment of hyperthyroidism is to render the patient euthyroid and off drug therapy. However, all of the three forms of treatment of hyperthyroidism i.e. antithyroid drugs, surgery and radioiodine therapy, fail to achieve this objective.

Radioiodine is increasingly considered the treatment of choice because of its safety and ease of administration (25). The major event of radioiodine therapy is thyroid failure; hypothyroidism may develop many years after the patient has been rendered euthyroid by radioiodine (26), so that long-term follow-up of thyroid function is essential.

In the present study, we observed that the numbers of abnormal serum TSH concentrations occurring during nearly 10 years of follow-up were significantly greater in patients with hypothyroidism after radioiodine therapy, as compared with those on continuous long-term methimazole treatment. In a retrospective study, 32% of patients receiving levothyroxine replacement had abnormal TSH concentrations, while 92% of them had seen a health care provider the previous year (27). In the Colorado Thyroid Disease Prevalence Study of patients who reported taking thyroid medication, nearly 40% had an abnormal serum TSH level (21). Therefore, patients under replacement therapy may be at risk of organic consequences of under- and over-treatment. However, the extent of this problem may differ in various clinics and depends on the proper replacement therapy and patient education by physicians and the social and cultural behavior of the patients.

At the end of 10 years of follow-up, the difference in bone mineral density between MMI- and radioiodine-treated groups was not statistically significant. Thyroid hormones exert their effect on osteoblasts via nuclear receptors to stimulate osteoclastic bone resorption (28). Even a slight increase in thyroid hormones to a level of subclinical hyperthyroidism results in accelerated bone turnover and calcium excretion (29). Of interest is the report of a decrease in bone turnover and conversion of the mineral balance to positive early during antithyroid treatment of patients with hyperthyroidism (30). Although bone turnover will increase following the early decline during antithyroid treatment (31), there are no reports of changes in bone mineral density during long-term continuous antithyroid drug therapy.

Important changes in hemodynamic regulation may occur in both clinical and subclinical thyroid diseases and treatment of these conditions may prevent cardiac



**Figure 2** The relative risk and confidence interval (CI) of the derangements in TSH secretion during follow-up and the rates of occurrence of goiter, serum antithyroperoxidase antibody above 100 IU/l, hypercholesterolemia above 200 mg/dl, hyper LDL-cholesterolemia over 130 mg/dl and osteoporosis defined as bone mineral density (BMD) below 1.5 standard deviation of Z score at the final visit in the continuous MMI-treated patients (group 1), as compared with the radioiodine-treated patients (group 2).

dysfunction and improve the quality of life (32–34). In the present study cardiovascular hemodynamic data were within the normal range and comparable in the two study groups.

This study had a few limitations. First, patients were selected from those aged over 40 years with diffuse toxic goiter, who had recurrence of hyperthyroidism after initial treatment with antithyroid drugs for one and a half years, and the results cannot be applied to all patients with hyperthyroidism, in particular, to the more common younger Graves' patients. Secondly, the drop-out rate of this study was rather high and might have affected the results. Thirdly, the number of patients available for study was not powered to detect significant differences in cardiovascular, bone and lipid alterations between the treatment groups. Fourthly, we were not able to investigate changes in immunological features during follow-up. Fifthly, the cost comparison is based on the need for follow-up in groups 1 and 2 being the same – every 6 months – but some clinicians may argue that group 1 patients needs more frequent follow-up than those in group 2. In addition, 9 patients required an additional radioiodine dose, which added to the cost in group 2 and may have been avoided by the administration of larger doses of radioiodine.

In spite of almost 60 years experience in the use of antithyroid drugs and radioiodine for the treatment of Graves' disease, the rationale for choice of therapy is often obscure (6, 35). Very often the choice has to be made between prolonged treatment with antithyroid drugs on the one hand and lifetime therapy with thyroid hormone for thyroid failure on the other (36).

The major drawback of antithyroid drug treatment for hyperthyroidism is the frequent reappearance of hyperthyroidism when therapy is discontinued. How-

ever, there is, of course, no need to discontinue antithyroid drug therapy, but rather this therapy can be continued indefinitely. Except for mild side effects, serious reactions are rare (37), and the risks of occurrence of cardiac and bone complications are equal to or less than those of radioiodine therapy. The cost of long-term continuous antithyroid drug therapy does not exceed that of the continuous care given following radioiodine therapy. Therefore, a possible approach to the therapy of hyperthyroidism may be to control the disease, for a lifetime, with antithyroid drugs. The remarkable lack of MMI side effects and the apparent high treatment compliance in this study prompt the adoption of an alternative approach such as this.

## Acknowledgements

We are indebted to Mrs Niloufar Shiva for English editing, Ms Mojgan Padyab for statistical help and Mrs Tahereh Fakhimi for preparation of the manuscript.

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Received 18 January 2005

Accepted 4 February 2005