Original Article

Long-term Continuous Methimazole or Radioiodine Treatment for Hyperthyroidism

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Abstract

Background: There is no general agreement as to which treatment is best for hyperthyroidism. The objective of this study is to investigate the effectiveness of continuous methimazole (MMI) treatment and to compare the results of neuropsychological testing in patients receiving long-term continuous MMI to those on replacement thyroxine following radioiodine-induced (RAI) hypothyroidism.

Methods: We enrolled 239 patients with diffuse toxic goiter who had recurrences of hyperthyroidism. Of these, 104 patients were randomized into two groups, MMI and treatment with thyroxine following RAI hypothyroidism. The remaining 135 patients voluntarily enrolled into either of the two groups. From all patients, 59 MMI-treated patients and 73 patients in the RAI group completed follow up. Thyroid function tests, serum lipids and lipoproteins, echocardiography, bone mineral density (BMD) and seven neuropsychology tests were performed at the final visit.

Results: In the RAI group compared to the MMI-treated group during a mean of 14 years follow up, there were more incidences of elevated TSH [> 5 mU/L; adjusted relative risk (RR) 1.23; 95% confidence interval (CI) 1.04–1.47), increased triglycerides (> 150 mg/dL; RR 2.20; 95% CI 1.34–3.62), HDL-C (< 40 mg/dL; RR 3.46; 95% CI 1.40 – 8.53), and early diastolic annular velocity (< 12.2 cm; RR 3.91; 95% CI 1.42–10.74), in addition to a decreased early diastolic to annular velocity ratio (< 6.7; RR 7.14; 95% CI 1.38–34.48). The MMI group scored better in neuropsychology tests that included mood, direction, logical memory, repeated numbers, and intelligence quotient (IQ).

Conclusion: Long-term MMI treatment was superior to RAI therapy in patients with diffuse toxic goiter when mood, cognition, cardiac function and occurrence of thyroid dysfunction were compared.

Trial Registration: Iranian Registry of Clinical Trials: IRCT 201009224794N1.

Keywords: Antithyroid drugs, hyperthyroidism, methimazole, radioactive iodine

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Introduction

Increasing reliance on radioiodine treatment for hyperthyroidism has been attributed to vascular morbidity, especially the risk of atrial fibrillation, and cardiovascular and cerebrovascular mortality associated with hyperthyroidism,[1] along with the occurrence of rare but serious complications during treatment and the high relapse of hyperthyroidism following discontinuation of antithyroid therapy. However, several large cohort studies have reported increased mortality from vascular causes in radioiodine-treated patients[2,3]; although it has been proposed that the underlying hyperthyroidism, rather than radioiodine itself, may be responsible for increased vascular mortality.[4] In addition, there may be an increased cancer incidence and mortality in radioiodine-treated hyperthyroid patients.[5]

It has been shown that the development of hypothyroidism after treatment with radioiodine abolishes the risk of vascular mortality.[2,4] These findings along with the cost-benefit of radioiodine have supported the recommendation of induction of hypothyroidism in hyperthyroid patients with the use of large doses of radioiodine. However, this type of practice increases the rate of hypothyroidism to 90%–100% from a rate of 50%–70% in those patients who receive low doses of radioiodine treatment.[6]

Several studies have shown that 30%–40% of patients receiving levothyroxine replacement have abnormal TSH levels[7]; therefore, patients under replacement therapy may be at risk for the health consequences of subclinical hyper- or hypothyroidism. Some studies have shown that subclinical hypothyroidism may cause alterations in cognitive function, mood, memory, and general health status,[8] and may be associated with an increased risk of coronary hearth disease.[9] Subclinical hyperthyroidism may increase the risk of atrial fibrillation[10] and low bone density.[11]

We have previously reported that in patients with recurrence of hyperthyroidism after discontinuation of antithyroid drugs, long-term continuous treatment with methimazole (MMI) was safe. The expense of treatment and complications from MMI did not exceed those of radioactive iodine therapy.[12] The aim of this study was to further investigate the effectiveness of continuous MMI treatment and to compare the results of neuropsychological testing in patients who received long-term continuous MMI to those patients on replacement thyroxine doses following radioiodine-induced (RAI) hypothyroidism.

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Table 1. List of health status and neuropsychology tests employed in this study and their domain of assessment.

Name of test	Assessment
Short Form Health Survey Questionnaire (SF-36)	General health
General Health Questionnaire (GHQ28)	Mental disorders
Rey Complex Figure Test (CFT)	Cognitive processes
Bender Gestalt Test (BGT)	Cognitive ability
Wechsler Memory Scale-Revised (WMSR)	Memory
Hospital Anxiety and Depression Scale (HADS)	Psychological distress
Symptom Checklist-90 (SCL-90)	Psychological distress
Wechsler Adult Intelligence Scale-Revised (WAIS-R)	Intelligence quotient (IQ)

Table 2. General characteristics and biochemical findings in methimazole (MMI) and radioiodine (RAI)-treated patients, at final visit.

Variable	Women			Men			All			Adjusted *p*-value*
	MMI (*n* = 41)	RAI (*n* = 62)	*P*	MMI (*n* = 18)	RAI (*n* = 11)	*P*	MMI (*n* = 59)	RAI (*n* = 73)	*P*	
Age (yr)	47.3 ± 15.4†	53.2±11.8	0.05	60.9 ± 13.5	52.5 ± 9.5	0.08	51.4 ± 16.1	53.1 ± 11.4	0.53	0.65
BMI (kg/m^2)	26.2 ± 3.5	27.7±4.7	0.02	27.5 ± 4.1	28.0 ± 4.1	0.68	26.2 ± 3.5	27.8 ± 4.5	0.04	0.14
Physical activity (*n*/%)										
Mild	23/56	47/76	0.05	8/44	9/82	0.12	31/53	56/77	0.009	0.12
Moderate	18/44	15/24	0.05	10/56	2/18	0.12	28/47	17/23	0.006	
Goiter grade (*n*/%)										
Zero	8/20	60/97	0.001	14/78	11/100	0.03	22/37	71/97	0.001	0.001
1 and 2	33/80	2/3	0.001	4/22	0/0	0.21	37/63	2/3	0.001	
Cholesterol (mg/dL)	190 ± 37	207 ± 29	0.01	198 ± 34	216 ± 55	0.31	192 ± 36	209 ± 34	0.01	0.025
Triglycerides (mg/dL)	109 (86–133)‡	163 (113–205)	0.008	139 (103–161)	167 (162–0)	0.008	115 (90–152)	167 (120–212)	0.001	0.001
LDL-cholesterol (mg/dL)	101 ± 23	111 ± 18	0.015	106 ± 24	117 ± 38	0.43	102 ± 23	112 ± 22	0.02	0.04
HDL-cholesterol (mg/dL)	54 ± 10	48 ± 10	0.011	49 ± 10	40 ± 14	0.045	52 ± 10	47 ± 11	0.005	0.002
TSH (mU/L)	2.8 (1.4–4.1)	1.4 (10.3–4.1)	0.164	4.0 (2.5–5.1)	2.9 (0.6–4.0)	0.16	3.1 (1.1–5.1)	1.7 (0.3–4.1)	0.012	0.80
TPOAb (IU/mL)	27 (7–82)	7 (5–15)	0.001	14 (8–34)	12 (6–16)	0.22	23 (7–42)	8 (5–15)	0.001	0.01
TRAb (U/mL)	2.0 (1.7–3.7)	1.8 (1.3–2.1)	0.09	1.9 (1.6–3.6)	2.1 (1.7–5.7)	0.72	2.1 (1.6–3.6)	1.8 (1.4–2.2)	0.025	0.87

* Adjusted for sex; †mean ± SD; ‡interquartile interval; BMI = body mass index; LDL = low density lipoprotein; HDL = high density lipoprotein; TPOAb = thyoperoxidase antibody; TRAb = TSH-receptor antibody.

Materials and Methods

Study design

This clinical trial was conducted between March 1989 and July 2009 in Tehran. The protocol of this study was approved by the Ethical Committee of the Research Institute for Endocrine Sciences and patients gave written informed consent. In the MMI group, 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 for a mean of 14.2 ± 2.9 years (range 5.7–20.3).

In the RAI group, patients received 100 μCi ^{131}I per gram of thyroid. The mean dose of radioiodine was 7.8 ± 4.9 mCi (range: 5–14 mCi). Those who became hypothyroid (after 1–3 doses of radioiodine) with thyrotropin (TSH) > 10 mU/L and free T_4 (fT_4) < 0.7 ng/dL were treated with levothyroxine to maintain serum TSH levels between 0.7–5.0 mU/L. Patients in this group were followed for a mean ± SD of 13.9 ± 3.1 years (range 5.2–19.6).

After monthly visits for the first three months of therapy, all patients in both groups were visited every three months for the first year and, every six months thereafter. At each visit, complete history was taken and physical examination was performed. Any adverse effects from the treatment were ascertained. Blood sample for cell blood count and the measurements of serum alanine aminotransferase, aspartate aminotransferase, T_4, triiodothyronine (T_3), fT_4, and TSH concentrations were obtained from each patient. Numbers of occurrences of thyroid dysfunction during the years of follow-up were recorded. Diagnoses of hypo- or hyperthyroidism, both overt and subclinical, were made based on the following criteria: euthyroid (TSH level 0.3–5.0 mU/L inclusive); hypothyroid (TSH > 5.0 mU/L and $fT_4 \leq 0.7$ ng/dL); subclinical hypothyroid (TSH > 5.0 mU/L, $fT_4 \geq 0.7$ ng/dL); hyperthyroid (TSH < 0.3 mU/L, $fT_4 > 2.0$ ng/dL, and/or $T_3 > 200$ ng/dL); and subclinical hyperthyroid (TSH < 0.3 mU/L, $fT_4 \leq 2.0$ ng/dL, and $T_3 \leq 200$ ng/dl). In all patients, the doses of MMI or levothyroxine were adjusted to maintain serum T_4 and T_3 concentrations within the middle range of normal values.

Study patients

We randomized 104 hyperthyroid patients that had experienced recurrent hyperthyroidism after discontinuation of antithyroid treatment[12]; all 51 patients who completed the study (26 patients in the MMI and 25 in the RAI groups) were included. In addition, another 135 patients with diffuse toxic goiter who had recurrence within two years after discontinuation of antithyroid therapy were

Table 3. Summary statistics and *P* values for neuropsychology tests.

Measure	MMI ($n = 59$)	RAI ($n = 73$)	*P*-value
SCL-90			
Compulsion			0.28
Normal and marginal	48 (81)*	61 (84)	
Abnormal	11 (19)	12 (16)	
Psychotic			0.046
Normal and marginal	53 (90)	61 (84)	
Abnormal	6 (10)	12 (16)	
WMSR			
Direction	5 (5–6)†	5 (4–5)	0.033
Logical memory	6 (4–7)	4 (3–6)	0.049
Repeating numbers	9 (8–11)	9 (8–11)	0.010
Memory score	96.6 ± 13.9	93.6 ± 15.2	NS
WAIS			0.02
Intelligence quotient (IQ)	107 ± 20	99 ± 15	

* Number in parentheses denote percentages; † Numbers are median (interquartile interval); ‡ Mean ± SD
SCL-90 = Symptom Checklist-90; WMSR = Wechsler Memory Scale-Revised; WAIS = Wechsler Adult Intelligence Score.

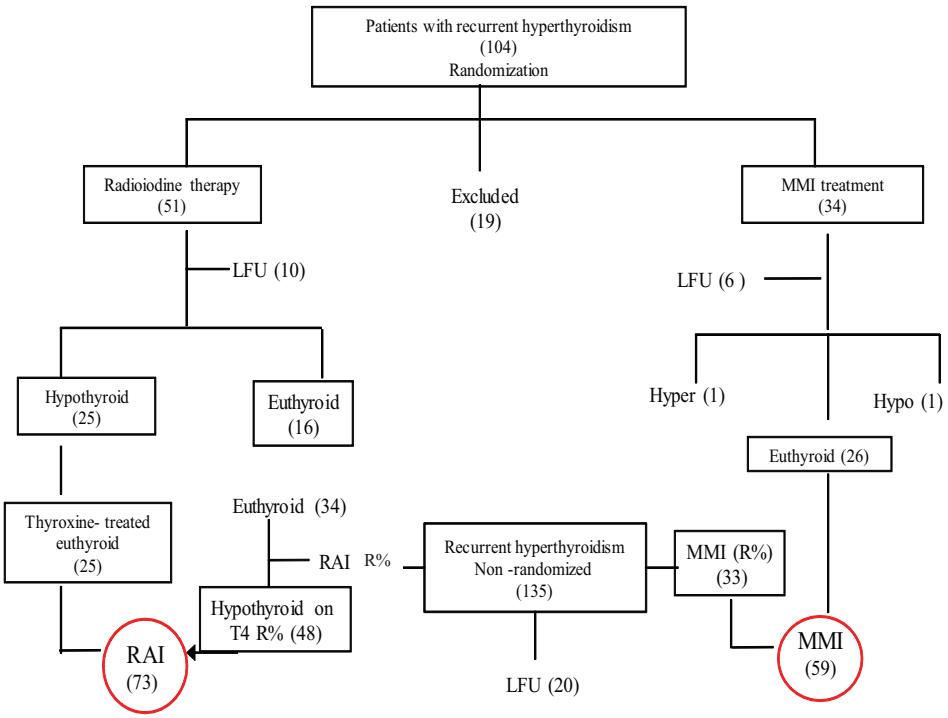

Figure 1. Schematic view of patients recruited for this study. Numbers in parentheses indicate numbers of patients in each group. LFU = lost to follow up; Hypo = hypothyroid; Hyper = hyperthyroid; RAI = radioiodine-induced hypothyroidism patients on levothyroxine treatment; MMI = methimazole; R% = treated.

assigned to either the MMI or RAI groups according to their preference, following full explanation of the effectiveness and complications of both modes of treatment. In total, 239 patients with diffuse toxic goiter were enrolled in this study. At the final visit, 33 were on continuous MMI treatment and 20 patients left follow up. Of those treated with radioiodine, 48 became hypothyroid and 34 remained euthyroid. In total, 132 patients (59 on long-term MMI and 72 RAI on thyroxine treatment) entered the present study (Figure 1).

Final visit

At the final visit, we measured height and weight and calculated body mass index (BMI). Patients underwent thorough physical examinations and their goiters were graded. The level of physical activity was evaluated by the LRC questionnaire.[13] Two questionnaires related to hypothyroidism[14] and hypethyroidism[15] were collected and the Short-Form Health Survey (SF-36)[16] in addition to seven neuropsychology tests[17] were conducted by four expert psychologists under the supervision of an attending psychiatrist (MB). Neuropsychological tests[17] are shown in Table 1 and included: General Health Questionnaire (GHQ28), Rey Complex Figure Test (CFT), Bender Gestalt Test (BGT), Wechsler Memory Scale-Revised (WMSR), Hospital Anxiety and Depression Scale (HADS), Symptom Checklist-90 (SCL-90), and the Wechsler Adult Intelligence Scale-Revised (WAIS-R).

Blood samples after 10–12 hour overnight fast were obtained for

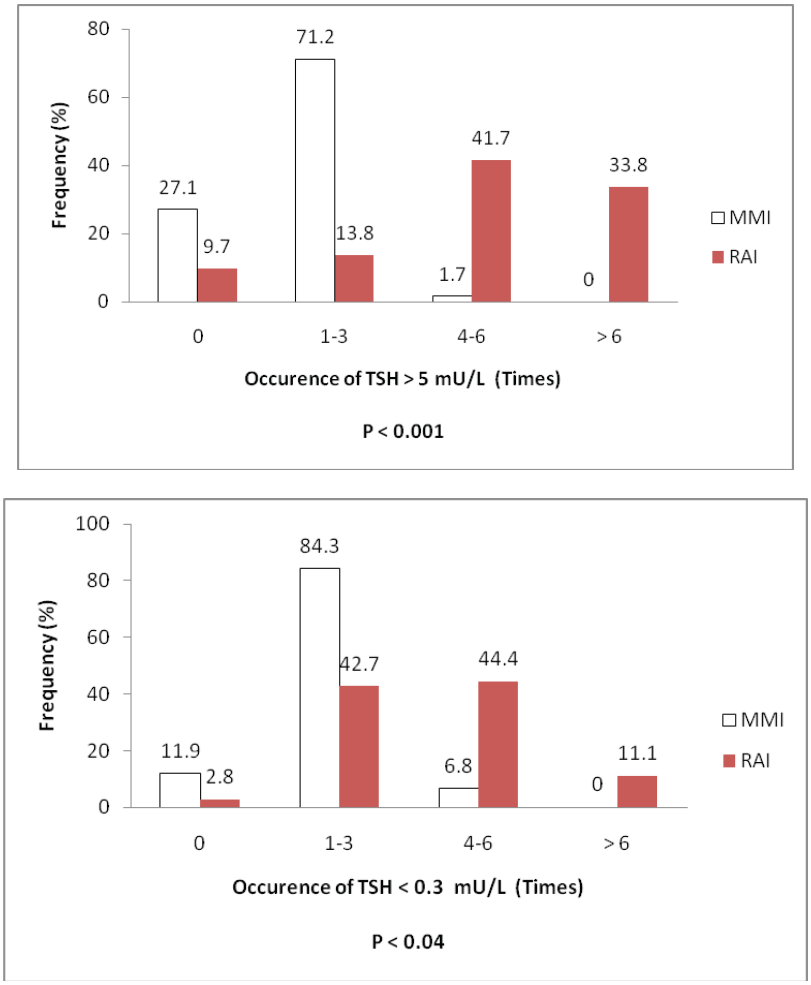

Figure 2. Frequency distribution of serum TSH > 5 and < 3 mU/L according to the number of times during 14 years of follow up in patients on continuous MMI treatment □ and radioiodine-induced (RAI) hypothyroid patients on levothyroxine treatment.
P < 0.001 for TSH > 5 mU/L and <0.004 after adjustment for sex; *P* < 0.04 for TSH < 0.3 mU/L and <0.06 after adjustment for sex.

measurements of lipid profile, fT_4, T_3, TSH, antithyroperoxidase (TPOAb), and TSH-receptor antibodies (TRAb). Serum fT_4 and T_3 were measured by radioimmunoassay and serum TSH by immunoradiometric assay using kits from Izotop (Budapest, Hungary). We measured TPOAb by immunoenzymometric assay (Monobind, Costa Mesa, CA, USA) and TRAb by immunoenzymometric assay (Bio Vendor Laboratory Medicine Inc., Czech Republic). The interassay coefficient of variations for all tests was less than 8% and intra-assay coefficient of variation for all tests was less than 10%. Reference ranges in euthyroid adults are: fT_4 (0.7–2.0 ng/dL); T_3 (80–199 ng/dL); TSH [0.3–5.0 mU/L (μU/mL)]; TPOAb (< 40 IU/mL); and TRAb (<1 negative; 1–1.5 gray zone; and > 1.5 U/mL positive).

Echocardiography using complete M-mode and two-dimensional Doppler tissue analysis was performed with an ultrasound mechanical system equipped with a 3.5 MHZ phased array transducer (Sonosite Micromaxx©).The echocardiography results were interpreted using guidelines from the European and American Associations of Echocardiography.[18] 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 and the femur (neck, trochanter, ward, and total). Precision errors, established with a local normal population, were less than 1.5% for all locations.

Costs were calculated from the actual ambulatory and hospital expenses incurred during the mean 14 years of follow up.

Statistical analysis

We estimated the sample size after a pilot study for the GHQ28 questionnaire. On the basis of difference of 7 points with a standard deviation of 12, power of 80% and α of 5%, the calculated sample size was 50 patients in each group. Baseline and outcome variables were compared with the use of Student's *t*-, Mann-Whitney, Chi-square, and Fisher's exact tests. To determine relative risk (RR), the number of patients with serum TSH < 0.3 and > 5 mU/L during follow up and those with goiter (TPOAb > 40 IU/mL, TRAb > 1.5 U/mL); BMD (< 1.5 SD of Z scores); early diastolic annual velocity (é) < 12.2 cm/sec and early diastolic velocity (E)/é ratio < 3.7; and the number of patients with serum cholesterol > 200 mg/dL, triglycerides > 150 mg/dL, LDL-C > 130 mg/dL, and HDL-C < 40 mg/dL at the final visit in both groups were considered. $P < 0.05$ was considered significant. Statistical analysis was performed using SPSS 9.05 software (SPSS Inc., Chicago, IL, USA).

Table 4. Summary statistics of echocardiography findings in the MMI and RAI groups.

Variable	MMI (n = 53)	RAI (n = 65)	Adjusted P-value
Left ventricular ejection fraction (%)	73.7 ± 8.9	76.6 ± 9.2	NS
Estimated pulmonary artery pressure (mm/Hg)	18.4 ± 6.8	16.6 ± 7.9	NS
Left ventricular mass index (gm/m^{2}BSA)	86.8 ± 61.0	88.79 ± 22.9	NS
Early diastolic mitral inflow velocity= E (cm/sec)	70.5 ± 20.4	67.3 ± 15.4	NS
Late diastolic mitral inflow velocity =A (cm/sec)	62.4 ± 16.2	67.7 ± 16.5	NS
E/A	1.23 ± 0.54	1.07 ± 0.43	< 0.001
Lateral annular velocity (cm/sec)= é	14.9 ± 4.3	11.5 ± 3.6	< 0.001
E/é ratio	5.83 ± 1.64	6.58 ± 1.88	< 0.001
Mitral deceleration time (msec)	195 ± 69	221 ± 70	0.048

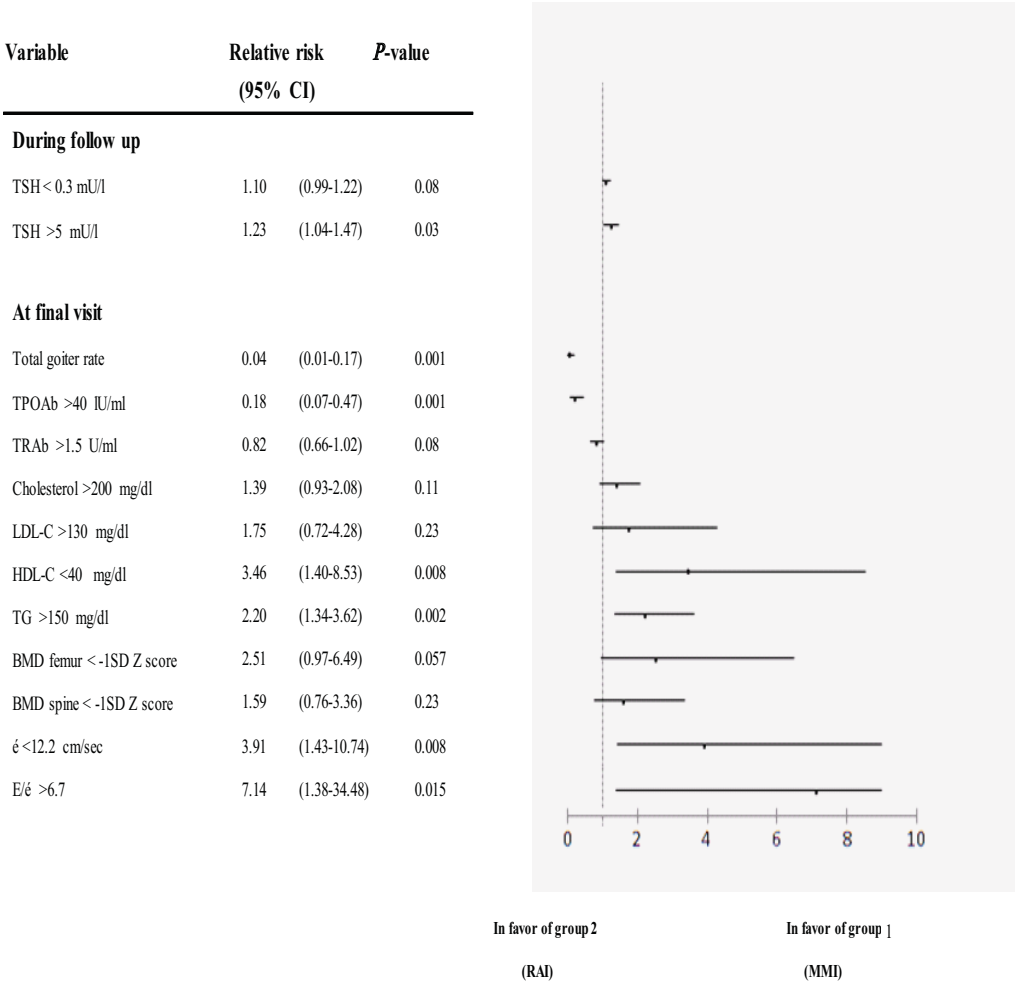

Figure 3. Relative risk (RR) and confidence interval (CI) of the study variables.
These include derangements in serum TSH during follow up and the rates of occurrence of goiter; serum antithyroperoxidase antibody (TPOAb) titer > 40 IU/L; serum TSH receptor antibody (TRAb) titer > 40 U/L; hypercholesterolemia > 200 mg/dL; hyper-LDL cholesterolemia > 130 mg/dL; hypertriglyceridemia > 150 mg/dL; hypo-HDL cholesterolemia < 1.5 mg/dL; bone mineral density (BMD) in the spine and femur < 1.5 SD Z score; diastolic annular velocity (é) and early diastolic (E)/é ratio in continuous MMI-treated patients (MMI group) compared with the radioiodine-induced (RAI) hypothyroid patients on levothyroxine treatment.

Results

There were no statistical differences in age, duration of symptoms, size of goiter, thyroid function tests, mean serum cholesterol, triglycerides, LDL-C, HDL-C, and echocardiographic findings in the 59 MMI treated and 73 RAI-treated patients at the time of study entrance. The events during follow up and findings on final visit were not statistically different between randomized and non-randomized patients in each group; therefore, data in both randomized and non-randomized patients in each group were pooled and appropriate comparisons applied for all participants.

Follow up

During a mean of 14 years follow up (range: 5.2–20.3 years), with the exception of minor allergic symptoms, no serious adverse events occurred. Patients in the MMI underwent 1287 thyroid

function tests and those in the RAI group underwent 1569 thyroid function tests. The median number of performed thyroid function tests was 22 (MMI) and 21 (RAI) per capita (range: 10–30). Figure 2 demonstrates the frequency of TSH levels > 5 and < 0.3 mU/L in both groups during the mean 14 years of follow up. There were more elevated TSH ($P < 0.001$) and suppressed TSH ($P < 0.04$) in the RAI group compared to the MMI group. After adjustment for sex, the difference in TSH > 5 mU/L remained significant, whereas TSH < 0.3 mU/L was marginally not significant.

The overall costs of management of hyperthyroidism during 14 years of follow up was 7,698,000 ± 31100 rials ($846 ± 34) in the MMI and 8,420,000 ± 34500 rials ($917 ± 38) in RAI-treated patients ($P < 0.001$).

Final visit

Patients' mean ages were 51.6 ± 16.1 years in the MMI group and 53.1 ± 11.4 years in the RAI group. There were 41 (69.5%) women and 18 (30.5%) men in the MMI group; whereas the RAI group comprised 62 (84.9%) women and 11 (15.1%) men ($P = 0.018$). Variables were adjusted with sex in all comparisons.

Table 2 lists some general and biochemical characteristics of 132 patients at the final visit. Although at the final visit the mean serum fT_4 and TSH concentrations did not significantly differ between the two groups, there were 32 (59%) MMI treated patients and 12 (16%) RAI-treated patients who had normal scores in the hypothyroid questionnaire ($P < 0.001$). Scores in the hyperthyroid questionnaire did not differ between both groups.

After adjustments for age, sex and BMI, TPOAb ($P < 0.001$) and serum HDL-C ($P < 0.002$) were higher in the MMI group. Serum cholesterol ($P < 0.025$), triglycerides ($P < 0.001$), and LDL-C ($P < 0.042$) levels were higher in the RAI group. The frequency of cholesterol levels over 200 mg/dl (5.17 mmol/L) was 34 vs. 72%; $P < 0.001$ and that of LDL-C (> 130 mg/dL; 3.36 mmol/L) was 23 vs. 53%; $P < 0.001$ in the MMI and RAI-treated groups, respectively. Serum TRAb levels were higher in the MMI treated group, however, the difference was not apparent after adjustment for sex.

Neuropsychological tests

Findings in the SF-36, GHQ28, CFT, BGT, and HADS were not significantly different between the two groups. In the SCL-90, there was no difference in compulsion, but there were more abnormal scores in the psychotic section of the test in the RAI group compared to the MMI group. In WMSR, scores of direction, logical memory, and repeating numbers favored the MMI group. Scores of WAIS showed that intelligence quotient (IQ) in MMI-treated patients was significantly higher than RAI subjects (Table 3).

Echocardiographic data

After adjustments for sex, percent ejection fraction, pulmonary artery pressure, left ventricular mass, the early diastolic (E) and late diastolic (A) velocities did not differ between groups. There was a higher early diastolic annular velocity (é) of 14.9 ± 3.4 in the RAI group versus 11.5 ± 3.6 cm for the MMI-treated group ($P < 0.001$) and mitral deceleration time 221 ± 70 msec in the RAI group compared to 195 ± 69 msec in the MMI-treated group ($P < 0.048$). As see in Table 4, the E/é ratio, an indicator of prediction of left ventricular pressures, was more favorable in the MMI (4.8 ± 4.3) compared to the RAI-treated groups (5.7 ± 1.8; $P < 0.02$).

Bone mineral density (BMD)

There were significant differences in BMD of the spine (L_2-L_4): 1.081 ± 0.20 vs. 0.996 ± 0.177 g/cm^2 ($P < 0.011$), T score: -0.61 ± 1.81 vs. -1.06 ± 1.00 SD ($P < 0.016$) and Z score: -0.318 ± -1.01 vs. -0.695 ± 0.909 SD ($P < 0.027$) in the MMI and RAI groups, respectively. These differences did not remain after adjustment for sex.

Relative risks (RR)

A comparison of RR of the variables between both groups showed a significant reduction in the number of patients with serum TSH > 5 mU/L (during follow up) and serum triglycerides > 150 mg/dL and HDL-C < 40 mg/dL and findings of echocardiogram, including é and E/é, ratio, (at final visit) were in favor of the MMI-treated, as compared to the RAI group. RR for total goiter rate and elevated TPOAb favored radioiodine treatment (Figure 3).

Discussion

Data in this study show that treatment of diffuse toxic goiter with continuous administration of MMI is safe, without major complications and accompanied by less events of subclinical hypothyroidism and dyslipidemia in comparison to levothyroxine-treated hypothyroidism induced by radioiodine. In addition, the results of the echocardiography and neuropsychology tests favor treatment with MMI over radioiodine.

There are four differences between the findings of the present article and our previous paper.[12] First, patients in this study were followed for the long-term; neuropsychological tests were not performed in the previous study; this study had a larger sample size; and the echocardiographic data were more detailed and newer indices calculated in the current study. The findings of fewer events of subclinical hypothyroidism and dyslipidemia in the MMI group in comparison to the RAI group were similar in both studies.

Ease, effectiveness and less expense of radioiodine therapy have led to increasing reliance on this method for treatment of hyperthyroidism.[19] The most frequent adverse event of radioiodine therapy is thyroid failure which may develop many years after the patient has been rendered euthyroid.[20] This event imposes the necessity of long-term follow up of thyroid function. In addition, reports of increased mortality from vascular causes, including cardiovascular and cerebrovascular deaths[2,3] and inconsistent data regarding cancer incidence and mortality following radioiodine treatment[5] have been of some concern.

The present study shows the potential benefits of continuous MMI therapy on mood, cognition, and psychological well-being compared to RAI treatment. It has been reported that subclinical hypothyroidism may cause alterations in cognitive function and mood alterations such as anxiety or depression and memory impairment, which improve with levothyroxine therapy.[8] However, one study has shown that patients on thyroxine replacement, even with normal serum TSH levels, demonstrate significant impairments in psychological well-being compared to control individuals.[21] We have shown that the number of events of subclinical hypothyroidism are significantly less in MMI-treated compared to RAI-treated patients. Therefore, some of the findings of the present study may well be related to intermittent hypothyroidism detected by increases in serum TSH in patients on levothyroxine treatment. A direct role of MMI on psychological well-being cannot be ruled out.

Thyroid hormones stimulate osteoblastic bone resorption[22] and slight increases in thyroid hormone concentrations to the level of subclinical hyperthyroidism have been shown to cause acceleration in bone turnover.[23] In addition, a decrease in bone turnover and conversion of the mineral balance to from negative positive during antithyroid therapy has been reported.[24] In the present study, BMD was higher in the MMI-treated group, but the difference did not remain after adjustment for sex.

Hemodynamic regulation may be altered in both clinical and subclinical thyroid disease. Treatment of these conditions may prevent cardiac dysfunction and decrease the rise of atrial fibrillation in patients with subclinical hyperthyroidism.[25,26] In the present study, findings of the echocardiogram regarding diastolic function favored MMI-treated compared to RAI-treated patients.

As expected, the MMI-treated group had a higher prevalence of total goiter rate. Of interest were the findings of higher levels of TPOAb. There were more patients with TPOAb > 40 IU/mL among MMI-treated patients while serum concentrations of TRAb were not significantly different between the two groups. Laurberg et al. have reported that the majority of patients with Graves' disease enter remission of TRAb within one year of medical or surgical therapy, while this remission is less common following RAI treatment; up to 20% of such patients have abnormal TRAb levels five years after treatment.[27] The present study reports the results of TRAb in patients treated with RAI after a median follow up of 14 years and shows TRAb levels to be within the normal range, comparable to those of MMI-treated patients.

The findings of the present study should be interpreted in view of the limitations of this work. First, the sample size was calculated for the GHQ28 questionnaire. We probably had limited power to detect significant differences in other variables. Secondly, patients were selected from those with diffuse toxic goiter who had recurrence of hyperthyroidism after initial treatment with antithyroid drugs. The findings cannot be extended to all patients with hyperthyroidism. Thirdly, almost half of the patients were randomized into two groups, whereas the other patients selected the study arm.

Despite over six decades of experience in treatment of hypothyroidism with antithyroid medications and radioiodine, there is a lack of consensus regarding the best treatment for hyperthyroidism. Surveys show that although most members of Thyroid Societies worldwide prefer antithyroid drugs as the first line of treatment for Graves' disease,[28] 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.[29] However, most of the thyroidologists agree that in patients with recurrent hyperthyroidism, the treatment of choice is radioiodine.

The major clinical drawback of treatment with antithyroid drugs is the 20%–70% relapse of hyperthyroidism when therapy is discontinued.[30] However, there is no need to discontinue antithyroid treatment, but rather this therapy can be continued indefinitely. The present study shows that with continuous MMI therapy there is high treatment compliance; serious adverse reactions are rare. Patients experience less periods of subclinical hypo- and hyperthyroidism and have a better psychological well-being with fewer alterations in serum lipids and echocardiographic findings compared to those who undergo RAI hypothyroidism and are on levothyroxine treatment.

In conclusion the results of this study indicate that lifetime continuous MMI therapy is superior to RAI therapy in many aspects and may be considered as an optimal method in the long-term treatment of patients with diffuse toxic goiter, particularly those who experience recurrence of hyperthyroidism after discontinuation of an effective antithyroid treatment.

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A view of Chalshotor Castle that was founded approximately 110 years ago during the Qajar period. The castle isa combination of Iranian and Europian architecture, and it is located near Shahr-e Kord inChaharmahaland Bakhtiari Province (photo by: M.H. Azizi MD, 2012)