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Treatment of Subclinical Hyperthyroidism in the Elderly: Comparison of Radioiodine and Long-Term Methimazole Treatment

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Background: This study aimed to compare the effectiveness and safety of radioiodine (RAI) and long-term methimazole (MMI) in the treatment of subclinical hyperthyroidism (SH) in the elderly.
Methods: From 306 patients, aged ≥65 years, with SH, 83 patients with thyrotropin <0.1 mU/L entered the study. In this randomized parallel-group trial, 41 and 42 patients were randomized to either RAI or long-term MMI treatment, respectively.
Results: In the RAI and MMI groups, 3 and 4 patients were excluded due to side effects, choosing other modes of treatment, and not returning for follow-up; 35 and 36 patients completed 60 months of follow-up, respectively. In the RAI group, 23 (66%) became hypothyroid, and 12 (34%) remained euthyroid 60 months after a fixed dose of 15 mCi RAI. In the MMI group, the starting dose was 10 mg daily and decreased to 4.9 ± 1.0, 4.3 ± 1.0, 4.4 ± 1.4, 4.3 ± 1.8, and 3.7 ± 1.3 mg after 1, 2, 3, 4, and 5 years of continuous MMI treatment, employing titration method. By the end of study, 34 (94%) patients were euthyroid and 2 patients with diffuse goiter developed spontaneous hypothyroidism with MMI treatment. Minor adverse events occurred in both groups in the first four months of treatment. No death or serious side effects were observed during 60 months of follow-up.
Conclusions: Both RAI and long-term low-dose MMI therapies are effective and safe for treatment of SH in the elderly.

Keywords: hyperthyroidism, methimazole, radioiodine, elderly

Introduction

Subclinical hyperthyroidism (SH), low serum thyrotropin (TSH) concentration with normal serum levels of both free thyroxine (fT4) and triiodothyronine (T3), may occur endogenously or caused by exogenous thyroid hormone use. The differential diagnoses of low serum TSH include severe nonthyroidal illness, pituitary/hypothalamic disease, psychiatric disease, and as a result of some medications (1). SH occurs in 1.8% of the population with higher rates in women and older individuals (2,3). Increased overall and cardiovascular mortality (4), nonfatal cardiovascular events (4,5), heart failure (6), cardiac arrhythmias (7), and osteoporosis and fractures (8,9), especially in older subjects and those with TSH <0.1 mIU/L, have been reported. Therefore, both the American Thyroid Association (ATA) and European Thyroid Association (ETA) guidelines recommend treatment of SH in individuals ≥65 years of age (10,11). ATA guidelines state that radioiodine (RAI) is considered appropriate for most patients especially the elderly in whom toxic multinodular goiter (MNG) is the most prevalent etiology of SH (10). However, studies dealing with efficacy and safety of various modes of therapy in SH are scarce in the elderly.

Antithyroid drugs (ATDs) and RAI therapy were introduced in the mid-1940s for management of hyperthyroidism (12,13). The major clinical problem with ATD therapy has been the 20–70% relapse of hyperthyroidism after discontinuation of therapy (10). Ease, effectiveness, and low expense of RAI therapy led to increasing reliance on this mode of treatment, which became the treatment of choice for hyperthyroidism in United States, while ATD therapy was the preferred modality in Europe, Japan, and some other countries of the world (14,15). In recent years, treatment of hyperthyroidism with ATD has increased in United States and this mode of therapy is employed for the majority of patients with hyperthyroidism (16,17).

Long-term continuous ATD treatment is effective and safe in both Graves' disease (18) and toxic MNG (19). The aim of

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this study was to examine the effectiveness and safety of long-term methimazole (MMI) treatment in comparison with RAI therapy in elderly subjects with SH.

Methods

Trial design

This randomized parallel-group clinical trial was conducted between September 2006 and February 2017 in a single endocrine clinic in Tehran, Iran, an iodine-sufficient area (20). Patients aged ≥65 years with grade 2 (severe) SH (TSH <0.1 mIU/L) were block randomized on the basis of goiter type (diffuse or nodular) to undergo RAI therapy or long-term MMI treatment for 60 months. Taking into account the inclusion criteria and the study design, the lengthy process of the study was explained in detail and approval for randomization was obtained. All patients had clinic visits every one to three months during the first year and every six months thereafter for the duration of study. The trial protocol was approved by the ethics committee of the Research Institute for Endocrine Sciences and informed consent was obtained from all participants.

Patients

Individuals who had the first diagnosis of SH were considered eligible if they had no previous treatment with RAI, thyroidectomy, or ATD. Key inclusion criteria were age ≥65 years, serum TSH <0.1 mIU/L at least on 2 occasions for 1–3 months, normal serum fT4 (9–23 pmol/L) and T3 concentrations (80–200 ng/dL), and no history or evidence of chronic kidney disease, cirrhosis, or cardiovascular disease. Key exclusion criteria were decreased thyroid uptake, serum T3 < 80 ng/dL, nonthyroidal illness, use of iodine and iodine containing substances such as amiodarone and radiological contrast materials, thyroid medications, moderate to high doses of glucocorticoids, mega doses of biotin and altered mental function. Diagnosis of diffuse and MNG was based on thyroid palpation and scintigraphy, and/or ultrasonography, and serum TSH receptor antibodies concentration.

Procedures

Information on baseline clinical characteristics such as age, sex, smoking history, and use of medications were obtained, and goiter size was estimated by palpation by an experienced thyroidologist (F.A.). At each visit, symptoms of thyroid dysfunction were assessed and a complete physical examination, including thyroid palpation and detection of signs of thyroid dysfunction, was performed. Serum fT4, T3, and TSH concentrations were also determined.

From 306 patients with SH, 223 patients with serum TSH concentrations of 0.1–0.39 mIU/L were excluded and 83 patients with serum TSH <0.1 mIU/L entered this study; 41 patients were randomized to receive RAI treatment; 3 chose other treatment modalities and 3 were lost to follow-up. To prevent any possible increase in serum thyroid hormone concentrations and unwanted adverse events after RAI treatment in the elderly, the remaining 35 patients received MMI treatment 20 mg daily until serum TSH increased to >0.4 mIU/L and/or serum fT4 and T3 levels were <15 pmol/L and <120 ng/dL, respectively. MMI was then discontinued; five days later RAI uptake of the thyroid was obtained (which was ≥16% in every subject) and a fixed dose of 15 mCi ^{131}I was administered. MMI treatment was not resumed after RAI, but careful assessment of every patient, in particular with regard to cardiac status and arrhythmia was performed for three to six months. The parallel group included 42 patients that received 10 mg MMI daily until serum TSH rose to >0.4 mIU/L. The titration method was then employed to adjust MMI dose to maintain serum fT4 between 10 and 23 pmol/L, serum T3 between 80 and 200 ng/dL, and serum TSH between 0.4 and 5.06 mIU/L. Four patients had minor adverse events and changed to other treatment modalities and two were lost to follow-up. The remaining 36 patients were treated with MMI for 60 months (Supplementary Fig. S1).

Additional treatment. When subclinical hypo- or hyperthyroidism occurred in the MMI group, the dose of MMI was adjusted. In the RAI group, when overt hypothyroidism (increased serum TSH with subnormal serum fT4) occurred, treatment with levothyroxine began and its dose was adjusted to keep serum TSH within normal range; those with subclinical hypothyroidism were not treated and not included in the numbers of patients who developed hypothyroidism. SH lasting for more than six months after the first RAI administration was treated with additional dose of RAI.

Final visit. At the final visit, we also measured bone mineral density (BMD), performed echocardiography and estimated total costs of treatment. BMD was assessed by dual-energy-X-ray absorptiometry with a Lunar DPX device (Madison, WI). Densitometry was performed on L1–L4 vertebral spine and neck, trochanter, and ward of the femur. Precision errors, measured with a local normal population, were less than 1.5% for all locations. Echocardiography was performed using complete M-mode and two-dimensional Doppler tissue analysis. An ultrasound mechanical system equipped with a 3.5 MHz phased array transducer (Sonosite Micromaxx©) was used. Results were interpreted using guidelines from the European and American Associations of Echocardiography (21). Costs were calculated from the actual ambulatory and hospital expenses incurred during five years of follow-up.

Definitions

Subclinical hypo- and hyperthyroidism were defined as normal serum fT4 (9–23 pmol/L) and T3 (80–200 ng/dL) concentrations with TSH >5.06 and <0.4 mIU/L, respectively. Grade 1 (mild) and grade 2 (severe) SH were distinguished through serum TSH 0.1–0.39 and <0.1 mIU/L, respectively. Overt hyperthyroidism was considered as TSH <0.4 mIU/L with fT4 > 23 pmol/L and/or T3 > 200 ng/dL, while overt hypothyroidism was considered as TSH >5.06 mIU/L with fT4 < 9 pmol/L.

The primary outcome measure was sustained euthyroidism up to the end of follow-up in each group. Secondary outcome measures were death, cardiovascular disease, and the occurrence of clinical and subclinical hypo- and hyperthyroidism until the end of study. Adverse events of MMI therapy, including skin reactions, arthralgia, agranulocytosis, and hepatic side effects, were monitored during long-term MMI treatment.

Table 1. Baseline Characteristics of the Study Patients According to the Treatment Group

Variables	*Radioiodine group (n = 35)*	*Methimazole group (n = 36)*	p
Age (years)	69.7 ± 4.1	69.6 ± 3.9	0.92
Male, *n* (%)	10 (28)	9 (25)	0.79
Current smoking, *n* (%)	5 (14)	4 (11)	0.73
Goiter weight (g)	48 ± 8	49 ± 7	0.58
Goiter type			0.81
Nodular, *n* (%)	19 (54)	21 (58)	
Diffuse, *n* (%)	16 (46)	15 (42)	
fT4 (pmol/L)	17.7 ± 1.6	17.2 ± 1.9	0.23
T3 (ng/dL)	162.3 ± 12	161.3 ± 16	0.77
TSH (mIU/L)	0.04 ± 0.03	0.04 ± 0.03	1.00

Data are mean ± standard deviation unless otherwise indicated. All characteristics were balanced between two study groups.
fT4, free thyroxine; T3, triiodothyronine; TSH, thyrotropin.

Statistical analyses

The sample size of the study was calculated based on the primary outcome measure to detect a 40% difference in attaining euthyroidism between 2 treatment arms (MMI vs. RAI) (19) with α of 0.05 and 90% power. Considering an attrition rate of 20%, a total sample size of 70 patients was needed for this trial. Baseline and outcome variables were compared with *t*-test and Fisher's exact test, for continuous and categorical variables, respectively. Data analysis was done based on initial treatment arm. Time to treatment success, that is, euthyroidism, was documented using Kaplan–Meier curves and Log-Rank test was used to compare the curves. A *p*-value of <0.05 was considered significant. Statistical analyses were performed using SPSS15 (SPSS, Inc., Chicago, IL).

Results

Baseline data

Seventy-one patients with mean (SD) age of 69.7 ± 4.0 years enrolled in this study. Clinical and biochemical characteristics of the two study groups are shown in Table 1. There was no significant difference in age, sex, smoking, goiter size, frequency of nodular goiter, and serum concentrations of fT4, T3, and TSH between RAI- and MMI-treated groups.

Effects of intervention

Radioiodine treatment. One year after RAI therapy, 15 (43%), 18 (51%), and 2 (6%) were hypothyroid, euthyroid, or had TSH <0.4 mIU/L, respectively. Three patients (1 with nodular goiter and 2 with diffuse goiter) had normal serum fT4 with elevated serum TSH concentrations of 5.6, 7.9, and 8.2 mIU/L 2–4 months after RAI therapy; however, serum TSH returned to normal range by the end of the first year of treatment in all 3 patients. By the end of the study, 23 (66%) were hypothyroid and 12 (34%) remained euthyroid (Table 2). Two patients required a second dose of RAI. Of 23 hypothyroid patients, 9 and 14 patients had nodular and diffuse goiter, respectively. While most of the euthyroid patients (10 of 12) had nodular goiter and only 2 of 16 patients with diffuse goiter were euthyroid, 5 years after RAI administration (Table 2). Mean estimated goiter weight decreased from 48 ± 8 to 30 ± 5 g ($p < 0.001$) by the end of the study.

MMI treatment. The starting dose of MMI was 10 mg/day. The mean daily requirement of MMI to maintain normal thyroid function was 4.9 ± 1.0, 4.3 ± 1.0, 4.4 ± 1.4, 4.3 ± 1.8, and 3.7 ± 1.3 mg after 1, 2, 3, 4, and 5 years after continuous long-term MMI therapy. By the end of first year of treatment, 34 (94%) were euthyroid, 2 (6%) persistent SH, and no patient was overtly hypothyroid. By the end of study, 2 patients with diffuse goiter had developed spontaneous hypothyroidism and 34 (94%) were euthyroid while on long-term MMI treatment (Table 3). Mean estimated goiter weight decreased from 49 ± 7 to 40 ± 6 g ($p < 0.002$) by the end of study. There was no significant association between baseline fT4, T3, or TSH with decrease in goiter size or decreasing dose of MMI over time.

Comparison of nodular goiter in two groups. After 5 years of intervention, all patients were euthyroid; 9 and 10 patients with and without levothyroxine therapy, respectively, in the RAI group and all 21 patients in the MMI group, while taking MMI treatment.

Comparison of diffuse goiter in two groups. Table 3 shows that 1 year after the study initiation, 11 of 16 patients (69%) became hypothyroid after RAI treatment and all 15 patients attained euthyroidism after MMI treatment. By the end of 5 years of treatment, hypothyroidism had occurred in 14 and 2 and euthyroidism was attained in 2 and 13 patients in RAI and MMI groups, respectively ($p < 0.001$).

Table 2. Number of Patients in Two Study Groups According to Thyroid Function Status During Five Years of Follow-Up

Years after intervention	*Radioiodine (n = 35)*			*Methimazole (n = 36)*		
	Hypothyroid[a]	*Euthyroid*	*TSH <0.4 mU/L*	*Hypothyroid*[a]	*Euthyroid*[b]	*TSH <0.4 mU/L*
First	15	18	2	0	34	2
Second	18	15	2	1	35	0
Third	21	13	1	1	34	1
Fourth	22	13	0	2	34	0
Fifth	23	12	0	2	34	0

[a]All hypothyroid patients were euthyroid by taking levothyroxine.
[b]Euthyroid patients in the MMI group were on daily MMI treatment.
MMI, methimazole.

Table 3. Thyroid Function Status of Two Study Groups According to the Goiter Type During Five Years of Follow-Up

	Radioiodine therapy						*Methimazole therapy*					
	Nodular goiter (n = *19*)			*Diffuse goiter* (n = *16*)			*Nodular goiter* (n = *21*)			*Diffuse goiter* (n = *15*)		
Years after intervention	*Hypo*[a]	*Eu*	*TSH <0.4 mU/L*	*Hypo*	*Eu*	*TSH <0.4 mU/L*	*Hypo*	*Eu*[b]	*TSH <0.4 mU/L*	*Hypo*	*Eu*[b]	*TSH <0.4 mU/L*
First	4	14	1	11	4	1	0	19	2	0	15	0
Second	5	12	2	13	3	0	1	20	0	0	15	0
Third	7	11	1	14	2	0	0	20	1	1	14	0
Fourth	8	11	0	14	2	0	1	20	0	1	14	0
Fifth	9	10	0	14	2	0	0	21	0	2	13	0

[a]All hypothyroid patients were euthyroid by taking levothyroxine.
[b]Euthyroid patients in the MMI group were on daily MMI treatment.
Eu, euthyroid; Hypo, hypothyroid.

Figure 1 demonstrates Kaplan–Meier curves for achievement of euthyroidism. Of 35 patients treated with RAI, only 12 (34%) patients became euthyroid without levothyroxine therapy and 23 (66%) patients were hypothyroid and treated with levothyroxine replacement. In the MMI group, 34 (94%) patients were euthyroidism from the first year to the end of 5 years with continuous long-term MMI treatment and only 2 patients (6%) were on levothyroxine replacement for hypothyroidism.

Bone mineral density. There was no significant difference in BMD of the spine and various parts of the femur in densitometry between the RAI and MMI groups before and after adjustment for sex.

Echocardiography data. Percent ejection fraction, pulmonary artery pressure, left ventricular mass, early diastolic and late diastolic velocities, and early diastolic annular velocity between the two study groups were not statistically different.

Overall costs. For management of hyperthyroidism and related complications, overall 5-year cost was 86,700,000 ± 1,068,000 rials ($7025 ± 89) and 84,100,000 ± 1,164,000 rials ($7008 ± 97) for RAI- and MMI-treated groups, respectively; the difference was not statistically significant.

Adverse events. No serious side effects such as death, cardiovascular complications, cancer, agranulocytosis, arthritis, or hepatic events occurred in either group during five years of follow-up. Anterior neck discomfort, palpitation, and nausea occurred in three patients after RAI administration. In the first four months of MMI treatment, one patient had liver enzyme elevation and three developed skin reactions and pruritus. Of these four patients, two chose RAI treatment and two were switched to propylthiouracil therapy.

Discussion

This article is the first randomized clinical trial comparing the effects of RAI and long-term MMI therapies in individuals ≥65 years with SH due to both nodular and diffuse goiters. Results showed that both methods could attain

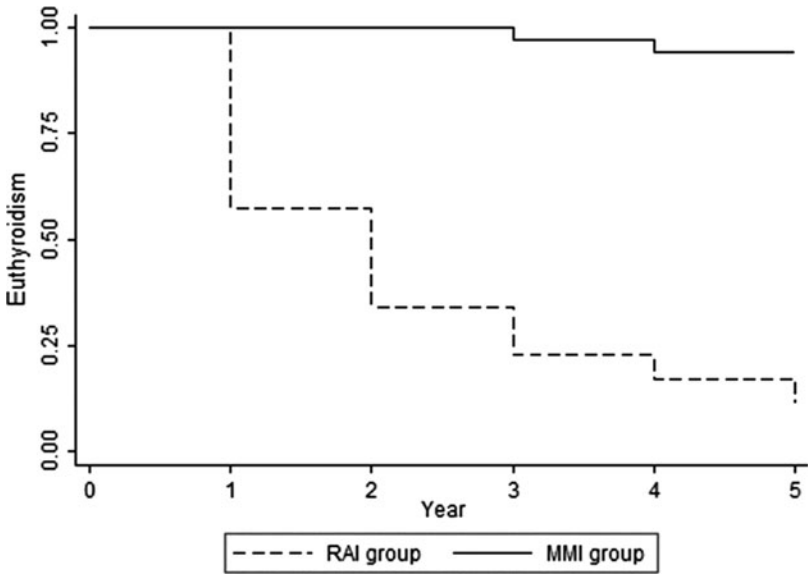

FIG. 1. Kaplan–Meier curves for attainment of euthyroidism in patients with subclinical hyperthyroidism treated with long-term MMI or RAI. The log-rank test showed a significant difference between 2 groups ($p < 0.001$). In the MMI-treated group, euthyroidism was maintained while the patients were continuously using MMI. MMI, methimazole; RAI, radioiodine.

euthyroidism with sustained surveillance. By the end of 5 years, all RAI-treated patients were euthyroid, 66% on levothyroxine and 34% without any treatment. All MMI-treated patients were also euthyroid, 94% on MMI and 6% on levothyroxine therapy.

Few studies have evaluated the effects of RAI and MMI in the treatment of SH. Nonrandomized studies have shown relative efficacy of both treatments in induction of euthyroidism and/or hypothyroidism in SH patients (22–28). Uncontrolled studies have reported beneficial effects of RAI treatment (23–25), antithyroid therapy (26) or beta-blockade (27) on cardiac measures. Other nonrandomized studies have shown that BMD of treated postmenopausal women with SH is more stable compared with untreated women (28,29).

There is paucity of randomized clinical trials assessing the effects of various modalities of treatment in elderly patients with endogenous SH. Since the risks of cardiovascular and skeletal diseases and mortality are increased in older subjects with SH (4,6–8), despite the absence of randomized prospective clinical trials, both ATA and ETA have recommended treatment in the elderly with grade 2 SH (10,11).

The goal of treatment for SH in the elderly is to normalize serum TSH concentrations without inducing adverse events. Owing to high relapse rates after discontinuation of 12–18 month ATD therapy, treatment of SH for individuals aged 65 years and older has not been preferred over RAI therapy (1,10,11). However, RAI treatment induces hypothyroidism in majority of patients over time and levothyroxine replacement may be accompanied by difficulties, in particular in the elderly (1,30).

In recent years, it has been shown that continuous long-term ATD treatment is both effective and safe (31,32). The rate of remission of Graves' hyperthyroidism after a minimum of 60 months treatment with MMI was 84% after 48 months of MMI withdrawal (33). In this study, we determined the diagnosis of endogenous grade 2 SH by ruling out other causes of suppressed TSH and transient SH. We measured serum total T3 because assays estimating fT3 is less well validated than those evaluating fT4 (34). We had a head-to-head comparison of RAI versus long-term MMI treatment. The primary outcome of study, euthyroidism, occurred in all MMI-treated patients, except two cases who developed spontaneous hypothyroidism. In the RAI group, one-third became euthyroid and two-third required levothyroxine therapies because of RAI-induced hypothyroidism. No serious adverse events were observed in either group during five years of follow-up.

We pretreated patients in the RAI group with daily 20-mg MMI until their serum TSH levels increased. This is not a universal practice and might increase the risk of subsequent hypothyroidism (35). We did not treat patients who developed subclinical hypothyroidism after RAI therapy since increased TSH may be transient after such therapy (36); likewise, the effects of levothyroxine treatment on cardiovascular risk and many other outcomes in the elderly with subclinical hypothyroidism are still unanswered (37).

Our findings show that long-term MMI treatment is a valid alternative to RAI in the treatment of the elderly with SH. Previous studies have demonstrated that variability of serum TSH in patients taking long-term MMI is significantly lower than those on levothyroxine treatment (38). In fact, serum TSH outside normal range has been observed in 30–50% of patients taking levothyroxine for maintenance therapy (18,39), while TSH variability is observed in only 13% in patients on long-term MMI treatment during 10.1 years of follow-up (18). In addition, impairment in psychological well-being (40), decreased resting energy expenditure (41), lower serum T3:thyroxine (T4) ratio, and increased total and low-density lipoprotein-cholesterol (42) have been reported in levothyroxine-treated patients when compared with normal controls. Lower T3:T4 ratio, higher BMI, and disturbed lipid parameters have also been reported in hypothyroid Graves' patients using levothyroxine compared with euthyroid Graves' individuals (43).

Based on the current study results, RAI leads more often to hypothyroidism and the need for levothroxine therapy, while MMI induces euthyroidism at the expense of continuation of MMI use. Clinically, there are relevant issues that may be appropriate in discussion of this trade-off before treating patients. In older patients levothyroxine requirements are lower than in younger ones, and a more conservative therapeutic goal should be considered to avoid overtreatment and exogenous hyperthyroidism (37). For older patients with SH due to Graves' disease, ETA prefers ATD treatment (11) and ATA recommends RAI therapy especially for older patients (10). Treatment with RAI is recommended by both associations for SH due to toxic adenoma and MNG because these patients are more likely to have persistent SH (10,11). Although this study shows that SH could be effectively treated with long-term MMI and a systematic review has shown the rarity of adverse events after the first year of MMI therapy (44), some physicians and patients may prefer ablative therapy over long-term MMI treatment. In addition, the underlying cause of SH should be taken into decision-making about the mode of treatment; almost all SH patients with either diffuse or nodular goiter attain euthyroidism on long term MMI, while the majority of SH patients with diffuse goiter and half of patients with nodular goiter become hypothyroid after RAI therapy and require lifelong levothyroxine treatment. Therefore, the choice of each treatment should be separately discussed regarding the underlying etiology of SH.

This study has several limitations. First, findings may not be extended to other populations and to patients with very large goiter. Second, the study was performed in patients aged ≥65 years without any chronic diseases and the findings may not apply to younger patients. Third, the sample size calculation was based on detection of 40% difference in attaining euthyroidism between two groups. This is rather a large difference and differences may be present with larger sample size. Fourth, baseline data on BMD and echocardiography were not available and differences in these data over the follow-up duration are not clear. Fifth, this study did not have a double-blind design and bias related to selection and attainment cannot be ruled out. Finally, an assessment of quality of life in patients in the two treatment groups was not performed.

We conclude that both RAI and long-term low-dose MMI therapies are effective and safe methods for treatment of SH in the elderly. Longer follow-up in patients receiving either mode of treatment may shed more light on the efficacy and safety for proper recommendation.

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Supplementary Material

Supplementary Figure S1

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