Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial

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Abstract

Objectives To determine whether thyroxine treatment is effective in patients with symptoms of hypothyroidism but with thyroid function tests within the reference range, and to investigate the effect of thyroxine treatment on psychological and physical wellbeing in healthy participants.
Design Randomised double blind placebo controlled crossover trial.
Setting Outpatient clinic in a general hospital.
Participants 25 patients with symptoms of hypothyroidism who had thyroid function tests within the reference range, and 19 controls.
Methods Participants were given thyroxine 100 µg or placebo to take once a day for 12 weeks. Washout period was six weeks. They were then given the other to take once a day for 12 weeks. All participants were assessed physiologically and psychologically at baseline and on completion of each phase.
Main outcome measures Thyroid function tests, measures of cognitive function and of psychological and physical wellbeing.
Results 22 patients and 19 healthy controls completed the study. At baseline, patients' scores on 9 out of 15 psychological measures were impaired when compared with controls. Patients showed a significantly greater response to placebo than controls in 3 out of 15 psychological measures. Healthy participants had significantly lower scores for vitality when taking thyroxine compared to placebo (mean (SD) 60 (17) *v* 73 (16), $P < 0.01$). However, patients' scores from psychological tests when taking thyroxine were no different from those when taking placebo except for a poorer performance on one visual reproduction test when taking thyroxine. Serum concentrations of free thyroxine increased and those of thyroid stimulating hormone decreased in patients and controls while they were taking thyroxine, confirming compliance with treatment. Although serum concentrations of free triiodothyronine increased in patients and controls taking thyroxine, the difference between the response to placebo and to thyroxine was significant only in the controls.
Conclusions Thyroxine was no more effective than placebo in improving cognitive function and psychological wellbeing in patients with symptoms of hypothyroidism but thyroid function tests within the reference range. Thyroxine did not improve cognitive function and psychological wellbeing in healthy participants.

Introduction

The classic symptoms of hypothyroidism are wide ranging and non-specific, therefore biochemical testing has become the cornerstone of diagnosis in patients for whom there is a clinical suspicion of thyroid dysfunction. However, recent anecdotal evidence has suggested there may be some clinical benefit in giving thyroxine to patients with symptoms of hypothyroidism who have thyroid function tests within the reference range.[1–3] After a series of reports in our local newspaper suggesting that such patients benefited from thyroxine therapy we treated two patients empirically with thyroxine, and they both reported symptomatic relief.[4]

To investigate this further, we conducted a double blind placebo controlled crossover trial of thyroxine in patients who had symptoms of hypothyroidism but whose thyroid function tests were within the reference range. A group of controls, who were similar in age and sex to the patient group, took part in a parallel trial. The same protocol was used for controls and patients to test the clinical belief that thyroxine treatment would have an effect on wellbeing even in participants without symptoms of hypothyroidism. We assessed response to thyroxine by using a battery of biochemical, physical, and psychological tests.

Methods

Participants

Patients were required to have had at least three of the following symptoms for six months: tiredness, lethargy, weight gain or inability to lose weight, intolerance to cold, hair loss, or dry skin or hair. We recruited patients either by referral from their general practitioner or hospital clinician, or through an article, published in a

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P+ *Details of baseline measurements and scores are available on the BMJ's website*

local newspaper, which described the trial and asked for volunteers. Controls were healthy volunteers recruited by personal contact with the investigators. All participants were required to have no current medical disorder, no history of thyroid disease, and recent thyroid function tests within the reference range.

Because of limited resources, the number of patients was restricted to the first 25 who met the criteria. Three patients withdrew at an early stage: one was anxious about the thyroxine dosage, one was ill, and the third failed to attend for unknown reasons. We did not enter one interviewed patient into the study because she was unwilling to have a thyrotrophin releasing hormone test. Unfortunately, we were unable to recruit sufficient controls to match the patients strictly for age and sex. However, the control group was similar to the patient group (see table A on the *BMJ*'s website). No controls were ineligible and all completed the study. The local ethical committee approved the study and we obtained informed consent from all participants.

Study protocol

The study was a randomised double blind placebo controlled crossover trial. The two treatment periods of twelve weeks each were separated by a washout period of six weeks. Half of the participants were given thyroxine for the first treatment period and placebo for the second treatment period; half were given placebo first and thyroxine second. The first 20 participants received the treatment in 100 μg capsules; thereafter 100 μg tablets were supplied. In each case a visually identical placebo was used. A 14 week supply of tablets, to be taken once a day, was provided for each phase and participants were asked to bring the remaining tablets to their assessment to assess compliance.

Randomisation was by toss of a coin in batches of four. Controls and patients attended their baseline assessment simultaneously, which led to unequal sequence groups. Two of the patients who withdrew had been assigned to the thyroxine-placebo group. The code was broken to two investigators (MAP and KMD) after each participant had completed the trial.

Table 1 Response to thyroxine of 22 patients with symptoms of hypothyroidism but thyroid function tests within the reference range. Values are mean (SD) unless otherwise stated

Outcome	Thyroxine	Placebo	Adjusted difference† (95% CI)	P value
Biochemical measures				
Thyroid stimulating hormone (mU/l)	0.66 (0.77)	1.77 (1.21)	−1.17 (−1.76 to −0.59)	<0.001***
Free thyroxine (pmol/l)	17.95 (3.03)	13.68 (3.37)	4.75 (2.67 to 6.83)	<0.001***
Free triiodothyronine (pmol/l)	3.72 (0.66)	3.50 (0.54)	0.23 (−0.11 to 0.56)	0.177
Cholesterol (mmol/l)	6.33 (1.17)	6.27 (1.25)	0.05 (−0.27 to 0.37)	0.739
Prolactin (mU/l)	250 (156)	307 (331)	−37 (−189 to 116)	0.622
Clinical measures				
Pulse (beats/min)	86 (14)	85 (16)	−1 (−7 to 6)	0.776
Blood pressure (mm Hg)	83 (12)	80 (12)	1 (−5 to 8)	0.657
Weight (kg)	84 (19)	83 (19)	1 (−1 to 2)	0.389
Cognitive functioning scores				
Logical memory I	25 (7)	25 (7)	−1 (−3 to 1)	0.231
Logical memory II	22 (8)	21 (7)	0 (−2 to 3)	0.965
Verbal paired associates I	20 (3)	19 (4)	0 (−1 to 2)	0.599
Verbal paired associates II	7 (1)	7 (1)	0 (−1 to 0)	0.671
Visual reproduction I	30 (7)	32 (6)	−1.9 (−3.3 to −0.4)	0.016*
Visual reproduction II	27 (8)	27 (8)	1 (−2 to 3)	0.594
Digits forward	10 (1)	9 (2)	1 (0 to 1)	0.133
Digits backward	8 (3)	8 (2)	0 (−1 to 1)	0.985
Trail making test	81 (31)	80 (31)	1 (−9 to 12)	0.779
Psychological functioning scores				
Hospital anxiety and depression scale	15 (10)	15 (8)	0 (−4 to 5)	0.874
SF-36 health survey:				
Role emotional	48 (47)	64 (44)	−18 (−48 to 12)	0.220
Physical functioning	46 (32)	46 (34)	0 (−14 to 14)	0.979
Role physical	36 (41)	43 (40)	−8 (−33 to 17)	0.515
General health	42 (24)	48 (24)	−6 (−17 to 4)	0.228
Vitality	36 (27)	42 (28)	−5 (−24 to 14)	0.571

*P<0.05. ***P<0.001.
†Adjusted by subject and period effects.

Evaluation

Serum thyroid stimulating hormone, free thyroxine, free triiodothyronine, cholesterol, and prolactin were measured at each visit. At baseline, serum ferritin and antithyroid peroxidase antibodies were measured and a thyrotrophin releasing hormone test was performed. Physiological and psychological assessments were performed at baseline and on completion of each phase.

At the end of the trial participants were asked to identify which treatment they thought they had received in each phase.

Biochemical measurements

Serum thyroid stimulating hormone, free thyroxine, cholesterol, and prolactin were analysed at the time the blood was collected. All blood samples were stored at −80°C and free triiodothyronine, ferritin, and antithyroid peroxidase antibodies were analysed in single batches to minimise interassay variation. Serum thyroid stimulating hormone, free thyroxine, free triiodothyronine, prolactin, and ferritin were measured by fluorescent microparticle enhanced immunoassay (Abbott Laboratories Ltd, Maidenhead, UK). An increment in thyroid stimulating hormone of >25 mU/l constituted an abnormal result in the thyrotrophin releasing hormone test. Antithyroid peroxidase antibodies were measured by a solid phase chemiluminescent enzyme immunoassay (DPC, Llanberis, UK). Cholesterol was measured on a multichannel discrete analyser (Olympus Diagnostica, Hamburg, Germany) using a cholesterol oxidase method (Randox Laboratories Ltd, Co. Antrim, UK). Interassay coefficients of variation were <15% for thyroid stimulating hormone, <9% for free thyroxine, <8.5% for free triiodothyronine, <6% for prolactin, and <2% for cholesterol.

Physical and psychological evaluation

We recorded supine blood pressure and pulse of participants using a Criticare (CE1023, Waukesha, WI, USA) non-invasive blood pressure monitor after they had rested for five minutes. We measured their weight on SECA scales (Hamburg, Germany).

We measured cognitive functioning with logical memory, verbal paired associates, visual reproduction, and digit span tests from the revised Weschler memory scale.[5] These tests assess attention and concentration, visual memory, and verbal memory. Psychomotor speed, attention, and sequencing were assessed by the trail making test.[6]

Psychological and physical wellbeing were measured by using two questionnaires. The hospital anxiety and depression scale assessed emotional disorder[7] and the SF-36 health survey measured five health concepts.[8] Two patients failed to complete one page of

the SF-36 health survey. We calculated the missing values by taking the means of their scores on their remaining two visits.

Statistical methods

Baseline characteristics were summarised by means (SD) or counts and percentages as appropriate. For each variable, participants were grouped into their sequence group (thyroxine-placebo or placebo-thyroxine) to create data summaries in relation to treatment.

In each set of participants, the effect of treatment on each variable was studied by using analysis of variance models in relation to patient, period, and treatment. The within patient treatment differences were adjusted by period and 95% confidence limits created. Some of the results were not normally distributed; therefore we repeated all analyses using non-parametric tests and rank data.

The placebo effect was calculated by using participants who received placebo as their first treatment. We calculated changes from baseline by subtracting the baseline value from placebo response.

Results

Baseline measures

All participants had thyroid function results within the reference range, with the exception of one patient who had a concentration of thyroid stimulating hormone of 5.8 mU/l (see table A on *BMJ*'s website). Concentrations of the hormone in this patient, however, normalised to 4.5 mU/l when taking placebo. Other biochemical tests for the same patient were within the reference range. Three participants—the patient described above, one control, and one patient who failed to complete the study—had exaggerated responses to thyrotrophin releasing hormone and raised concentrations of antithyroid peroxidase antibodies (range 262-1656 U/ml). One patient and one control had raised concentrations of antithyroid peroxidase antibodies (211 U/ml and 76 U/ml, respectively) but normal thyrotrophin releasing hormone responses.

Patients' scores on psychological testing were significantly impaired for logical memory I and II, trail making test, hospital anxiety and depression scale, and all components of the SF-36 health survey in comparison to healthy participants (see table B on *BMJ*'s website).

Response to thyroxine or placebo

Biochemical measures

In both groups the serum concentrations of thyroid stimulating hormone decreased and free thyroxine increased in response to thyroxine, confirming compliance with treatment. Although free triiodothyronine concentration increased in both groups when participants were taking thyroxine, the difference between the response to placebo and the response to thyroxine was only significant in the healthy group (tables 1 and 2). This finding was replicated by non-parametric analysis of the data. The response to thyroxine in patients with positive autoantibodies or abnormal thyrotrophin releasing hormone responses did not differ from that in other participants; numbers were too small for detailed analysis. No other significant biochemical changes were observed.

Table 2 Response of 19 healthy participants to thyroxine. Values are mean (SD) unless otherwise stated

Outcome	Thyroxine	Placebo	Adjusted difference† (95% CI)	P value
Biochemical measures				
Thyroid stimulating hormone (mU/l)	0.32 (0.38)	1.55 (1.54)	–1.17 (–1.80 to –0.53)	0.001**
Free thyroxine (pmol/l)	20.21 (4.33)	14.29 (5.10)	5.83 (2.02 to 9.63)	0.005**
Free triiodothyronine (pmol/l)	4.39 (1.03)	3.62 (0.52)	0.82 (0.34 to 1.31)	0.002**
Cholesterol (mmol/l)	5.03 (0.84)	5.22 (0.78)	–0.21 (–0.46 to 0.04)	0.095
Prolactin (mU/l)	196 (71)	211 (118)	–14 (–73 to 46)	0.636
Clinical measures				
Pulse (beats/min)	77 (12)	75 (12)	3 (–2 to 8)	0.222
Blood pressure (mm Hg)	74 (9)	72 (11)	3 (–3 to 9)	0.358
Weight (kg)	66 (12)	67 (12)	–1 (–1 to 0)	0.240
Cognitive functioning scores				
Logical memory I	34 (5)	33 (6)	1 (–1 to 4)	0.380
Logical memory II	31 (7)	31 (6)	1 (–2 to 3)	0.435
Verbal paired associates I	20 (3)	21 (3)	–1 (–1 to 0)	0.128
Verbal paired associates II	7 (1)	7 (1)	0 (–1 to 0)	0.413
Visual reproduction I	35 (4)	36 (2)	–0.8 (–1.8 to 0.3)	0.148
Visual reproduction II	34 (4)	34 (4)	0 (–1 to 2)	0.723
Digits forward	10 (2)	10 (2)	0 (–1 to 1)	0.605
Digits backward	8 (3)	9 (2)	0 (–1 to 0)	0.338
Trail making test	57 (19)	54 (12)	3 (–3 to 9)	0.368
Psychological functioning scores				
Hospital anxiety and depression scale	9 (7)	6 (5)	2 (0 to 5)	0.095
SF-36 health survey:				
Role emotional	82 (28)	92 (19)	–7 (–21 to 7)	0.318
Physical functioning	91 (14)	93 (10)	–1 (–6 to 3)	0.515
Role physical	79 (27)	89 (19)	–10 (–26 to 6)	0.216
General health	80 (12)	84 (10)	–5 (–11 to 2)	0.135
Vitality	60 (17)	73 (16)	–13 (–22 to –4)	0.007**

**P<0.01.
†Adjusted by subject and period effects.

Physical health and psychological measures

We compared the differences in the scores at baseline and after placebo in participants taking placebo first. The patients showed a significant symptomatic improvement in the general health, role physical, and hospital anxiety and depression scale scores after placebo, compared with healthy participants (mean (95% confidence interval) 8 (2 to 15) *v* −8 (−14 to −3), 25 (4 to 46) *v* −9 (−32 to 13), and −7 (−11 to −3) *v* −1 (−2 to 0), respectively; table 3). We observed no changes in measures of cognitive function. There was no placebo effect with regard to psychological or cognitive function scores for the controls (table 3).

In the comparison of the response to thyroxine or placebo, the only difference in cognitive function tests was in the patient group, which showed a significant improvement in visual reproduction I score with placebo (32 (6) *v* 30 (7), P = 0.016; table 1). The difference was less significant on non-parametric analysis (P = 0.035) and was not replicated in the delayed recall test, which suggests that the finding may be spurious. No other tests of cognitive or psychological function showed differences (table 1). The vitality score for the healthy control group was significantly better with placebo compared with thyroxine (73 (16) *v* 60 (17), P = 0.007; table 2), but otherwise no differences were observed.

Clinical measures

No significant changes occurred in patients with respect to blood pressure, pulse rate, or weight during the study.

Table 3 Effect of placebo when given first for patients with symptoms of hypothyroidism but thyroid function tests within the reference range and controls. Values are mean or mean difference (95% confidence intervals)

	Patients (n=14)			Controls (n=8)			Patients *v* controls (P value)
Outcome	**Baseline**	**Placebo**	**Placebo–baseline**	**Baseline**	**Placebo**	**Placebo–baseline**	
Biochemical measures							
Thyroid stimulating hormone (mU/l)	1.84	1.78	–0.06 (–0.47 to 0.35)	1.25	1.08	–0.17 (–0.42 to 0.08)	0.685
Free thyroxine (pmol/l)	13.93	14.50	0.50 (–1.75 to 2.75)	14.63	15.25	0.63 (–0.63 to 1.88)	0.932
Free triiodothyronine (pmol/l)	3.20	3.66	0.51 (0.17 to 0.84)	3.55	3.86	0.29 (–0.23 to 0.80)	0.407
Cholesterol (mmol/l)	6.19	6.20	–0.13 (–0.40 to 0.14)	4.99	5.14	0.15 (–0.28 to 0.58)	0.212
Prolactin (mU/l)	286	339	56 (–142 to 254)	240	193	–46 (–94 to 2)	0.419
Clinical measures							
Pulse (beats/min)	79	82	5 (–2 to 12)	68	72	5 (–4 to 13)	0.918
Blood pressure (mm Hg)	81	79	–2 (–6 to 1)	77	69	–8 (–18 to 3)	0.175
Weight (kg)	85	85	–1 (–2 to 1)	67	67	0 (–1 to 0)	0.627
Cognitive functioning							
Logical memory I	19	26	6 (3 to 9)	28	34	5 (–1 to 12)	0.801
Logical memory II	15	20	5 (2 to 8)	26	31	5 (–2 to 11)	0.777
Verbal paired associates I	16	19	3 (2 to 4)	19	21	2 (0 to 4)	0.211
Verbal paired associates II	7	7	0 (0 to 1)	8	8	0 (–1 to 1)	0.526
Visual reproduction I	32	34	2 (0 to 4)	35	36	1 (–2 to 4)	0.555
Visual reproduction II	28	29	1 (–3 to 5)	33	35	2 (–2 to 7)	0.655
Digits forward	9	9	1 (–1 to 2)	10	10	1 (0 to 1)	0.862
Digits backward	7	8	1 (0 to 2)	10	10	0 (–2 to 1)	0.124
Trail making test	97	82	–16 (–29 to –2)	65	53	–11 (–22 to –1)	0.655
Psychological functioning							
Hospital anxiety and depression scale	20	13	–7 (–11 to –3)	8	7	–1 (–2 to 0)	0.034*
SF-36 health survey:							
Role emotional	53	71	21 (–4 to 47)	79	80	1 (–17 to 19)	0.240
Physical functioning	42	50	8 (–7 to 23)	98	97	–1 (–2 to 1)	0.354
Role physical	18	45	25 (4 to 46)	97	88	–9 (–32 to 13)	0.031*
General health	40	50	8 (2 to 15)	94	86	–8 (–14 to –3)	0.001**
Vitality	29	47	16 (–4 to 35)	71	71	0 (–7 to 7)	0.214

*P<0.05. **P<0.01.

At the end of the study neither group was able to identify accurately which treatment period was thyroxine or placebo (table 4).

Discussion

This is the first randomised double blind placebo controlled trial of thyroxine treatment in patients who have symptoms of hypothyroidism but are biochemically euthyroid.

Biochemical results

Compliance was confirmed in both groups by the rise in free thyroxine and fall in thyroid stimulating hormone while participants were taking thyroxine. The lack of significant increase in free triiodothyronine in patients taking thyroxine might reflect impairment of the peripheral conversion of thyroxine to triiodothyronine. Although this finding requires further investigation, anecdotal evidence suggests that patients could benefit from thyroxine treatment alone.[9]

Comparison of thyroxine and placebo treatments

Psychological testing showed that patients differed from the controls at baseline. Cognitively, they scored worse on immediate and delayed verbal recall and had slower motor movements. They also perceived themselves to have poorer general health, more fatigue, increased problems with routine tasks and activities related to work, and higher levels of anxiety and depression. These findings may be consistent with a depressive illness, although no formal assessment was performed.

Controls showed no significant changes in psychological measurements after treatment with either thyroxine or placebo. This suggests that, contrary to widespread belief, thyroxine does not have a non-specific effect on wellbeing. In the participants who received placebo first, patients showed a small but significant improvement in general health, physical wellbeing, and anxiety and depression after placebo when compared with baseline. Thyroxine treatment, however, had no greater effect than placebo in this group of patients. This contrasts with previous studies in biochemically hypothyroid patients, where thyroxine treatment was associated with psychological improvement.[10–12]

Table 4 Participants' ability to distinguish between thyroxine and placebo at end of trial

	Patient group	Control group
Correct	9	6
Wrong	10	8
"Don't know"	3	5

Numbers in the study

The small number of participants in this preliminary study means that, although there was no significant difference between placebo and thyroxine in 13 of the 14 well validated psychological tests, the power of the study may not have been sufficient to eliminate definitively a possible biological effect of thyroxine. If this was the case we would have expected to see a trend in favour of thyroxine over placebo in the test results, especially as a recent open intervention study of thyroxine (mean dose 125 μg daily) reported self

What is already known on this topic

Recent anecdotal accounts suggest that patients with symptoms of hypothyroidism but who are biochemically euthyroid may benefit from thyroxine treatment

No controlled trials in this area have been reported

What this study adds

This study suggests that thyroxine is no more effective than placebo in improving psychological and physical wellbeing in patients who show symptoms of being clinically hypothyroid but whose thyroid function tests are within the reference range

Thyroxine replacement did not improve psychological and physical wellbeing in healthy participants

assessed improvements in energy and poor memory in 80% of 139 participants.[9] Our study showed no discernible trend (table 1).

Conclusion

We can find no support for the hypothesis that people with symptoms of hypothyroidism but thyroid function tests within the reference range benefit from treatment with 100 µg thyroxine daily. However, our results require confirmation in a larger study. The improvement noted anecdotally and in open studies may be due to the placebo effect shown in our study.

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Contributors: MAP conceived the study and coordinated the laboratory component. MAP, EHMcL, CJGK and KMD designed the study. KMD and KM chose the cognitive function tests and questionnaires, and KM tested all participants. AS coordinated all contact with the study participants and undertook the clinical assessment of the participants at each visit. ADMcM performed the statistical analysis and provided further statistical advice. All authors were involved in writing the paper, with MAP providing coordination. EHMcL is guarantor for the study.

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A patient who changed my practice

"That's very nice, but will it get me pregnant?"

I have to confess, I didn't understand the question at the time. A year later, I am starting to. I was an eager new general practitioner and member of a research team investigating how the internet might influence patients' use of primary care, and we had just begun offering free internet access at our deprived inner city practice. I had filled the waiting room with posters advertising the service, and a member of staff was on hand to guide newcomers through the web. With our new PC and a cup of coffee, we would help patients empower themselves with the information they'd been waiting for.

The patient's recent blood tests for infertility had indicated that she had polycystic ovary syndrome, and she had come for her follow up appointment. I explained the likely diagnosis, suggested she might use our internet service to find more detailed information, and offered to demonstrate what was available. Going straight to a website that I knew had some excellent patient information on the syndrome, I briefly talked her through it and gave her a printed copy to take away. She and I had always had a good rapport, I believed. Now she looked disdainfully, first at me and then at the sheets of paper I offered. "That's very nice," she said, "but will it get me pregnant?"

In my enthusiasm, I had completely misunderstood what the patient wanted from the consultation. She wanted to conceive and wasn't in the least interested in explanations of why she had failed to thus far—she had come to get a prescription, not information. However helpful our internet service was intended to be, she didn't want that kind of help. Neither, it seems, did many of our 13 000 patients, only nine of whom used the internet service in the three months before we closed it. (All but one of the nine were well educated, had good jobs, and had already used the internet—not representative of residents of inner city Manchester.)

Since this rather awkward encounter, I have noticed that many of my assumptions about what my patients want are equally mistaken. Very few want information from me. Many don't even want a prescription: they want money, or a job, or an escape from their often appalling lives. I think the internet is a valuable source of patient information, but I've been reminded of a maxim drummed into me by the first consultant who taught me clinical medicine: "Assume nothing about your patients—check everything, every time."

Our research group is conducting a questionnaire and interview study to investigate the influence of deprivation on attitudes to health information and the internet. Meanwhile, I persist in trying to persuade my patients to expect a little more from me than housing letters and prescriptions. But I try to assume less before opening my mouth or offering information.

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