PE1463/GGG

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The Scottish Government
Riaghaltas na h-Alba

LEGACY 2014
XX COMMONWEALTH GAMES
SCOTLAND

Sigrid Robinson
Assistant Clerk
Public Petitions Committee
Room T3.40
The Scottish Parliament
Edinburgh
EH99 1SP
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Your ref: PE1463
19 February 2016

Dear Ms Robinson,

Thank you for your letter of 9 February 2016 regarding the Public Petitions Committee's continued consideration of petition PE1463 (*Calling on the Scottish Parliament to urge the Scottish Government to take action to ensure GPs and endocrinologists are able to accurately diagnose thyroid and adrenal disorders and provide the most appropriate treatment.)*

I will deal with your questions in turn:

1. *The cost of the Thyroid UK's survey and why the commissioning document for the survey did not ask that Scottish data be able to be extrapolated from the UK-wide data collected;*

The cost of the listening exercise was £1,064.69. As there is no Scotland-only Thyroid third sector organisation, Thyroid UK agreed to carry out this work. The listening exercise posed a set of questions designed to seek patient views on particular aspects of their care. There were 5,129 respondents to the exercise. The results need careful consideration in terms of the experiences of those who responded.

We recognise and agree that there is an issue as to whether any responses are identifiable as people living or being treated in Scotland. We are following this up with Thyroid UK.

2. *The details of the clinical trials mentioned in relation to T3 and natural desiccated thyroid, including how many people were involved; when the studies were conducted; where the studies were conducted, and the outcome of those studies;*

Please refer to **Annex A** (pg 3) which lists the randomised clinical trials and meta-analyses of liothyronine. Findings of the randomised clinical trials are at **Annex B** (pg 5) and findings from the meta-analyses at **Annex C** (pg 19).

3. *A copy of any current SIGN or other guidelines on thyroid conditions for medical practitioners in Scotland.*

At present, there is no SIGN guideline for the treatment and diagnosis of hypothyroidism.

SIGN have considered that influencing availability of whole thyroxin and validating diagnostic tests was outwith their remit and they agreed that a good practice guide for general practice may be more useful. SIGN are therefore taking the proposal to the Royal College of Physicians through SIGN Council and we await their advice in due course. Scottish Government cannot influence this process.

There is a position statement by the British Thyroid Association (BTA), published in May 2015, which clearly sets out their recommendations on the management of primary hypothyroidism based on the current literature, review of the published positions of the European Thyroid Association (ETA) and American Thyroid Association (ATA), and in line with best principles for medical practice.

These recommendations have been endorsed by the Association of Clinical Biochemistry (ACB), British Thyroid Foundation (BTF), Royal College of Physicians (RCP) and Society for Endocrinology (SFE) and therefore reflects current best practice in the management of primary hypothyroidism.

A link to this BTA publication is attached at **Annex D** (pg 23).

I hope that this information is helpful.

Yours sincerely,

Elizabeth Porterfield
Head, Strategic Planning and Clinical Priorities

ANNEX A

Summary of randomised clinical trials of liothyronine

FIRST NAME AUTHOR	YEAR	NUMBER in TRIAL	OUTCOME SUMMARY	COMMENT
Bunevicius	1999	33	Improvement in mood and neuropsychological function	US
Smith	1970	99	No overall benefit with some adverse effects	UK Much older than the other studies
Bunevicius – (2)	2002	13	Improved mental functioning	US
Clyde	2003	46	No overall benefit	US
Walsh	2003	110	No overall benefit	Australia
Sawka	2003	40	No overall benefit	Canada
Siegmund	2004	26	No overall benefit. Concern about increased risk	Germany
Escobar-Morreale	2005	28	No overall benefit	Spain
Appelhof	2005	94	No overall benefit in trial outcomes, although some non-specific patient preference in combination therapy.	NL
Appelhof (2)	2005	94	No overall benefit in trial outcomes	NL
Rodriguez	2005	27	No overall benefit	US
Saravanan	2005	697	No conclusive evidence of specific benefit . Consistent with a subgroup of patients showing transient improvement	They also emphasize the large and sustained placebo effect UK
Nygaard	2009	59	Was superior to monotherapy by evaluating several QOL, depression and anxiety rating scales	DK
Valizadeh	2009	71	The data do not support the hypothesis that combined therapy improves the well-being	Iran
Fadeyev	2010	36	Lower cholesterol but increased risk of bone disease	Russia

TOTAL NUMBER OF PATIENTS INVOLVED IN THE STUDIES: 1473

Summary of Meta-analyses on the Use of liothyronine

FIRST NAME AUTHOR	YEAR	NUMBER OF TRIALS	TRIAL CONCLUSION
Escobar-Morreale	2005	9	Administration of levothyroxine alone should remain the treatment of choice for replacement therapy of hypothyroidism
Grozinsky-Glasberg	2006	11	T(4) monotherapy should remain the treatment of choice for clinical hypothyroidism
Joffe	2007	9	analysis reveals no significant difference in treatment effect on psychiatric symptoms in the nine controlled studies to date
Ma	2009	10	T4 alone replacement may remain the drug of choice for hypothyroid patients

FINDINGS OF RANDOMISED CLINICAL TRIALS OF LIOTHYRONINE

Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism.

Bunevicius R[1], Kazanavicius G, Zalinkevicius R, Prange AJ Jr.

Author information

Abstract

BACKGROUND:

Patients with hypothyroidism are usually treated with thyroxine (levothyroxine) only, although both thyroxine and triiodothyronine are secreted by the normal thyroid gland. Whether thyroid secretion of triiodothyronine is physiologically important is unknown.

METHODS:

We compared the effects of thyroxine alone with those of thyroxine plus triiodothyronine (liothyronine) in 33 patients with hypothyroidism. Each patient was studied for two five-week periods. During one period, the patient received his or her usual dose of thyroxine. During the other, the patient received a regimen in which 50 microg of the usual dose of thyroxine was replaced by 12.5 microg of triiodothyronine. The order in which each patient received the two treatments was randomized. Biochemical, physiologic, and psychological tests were performed at the end of each treatment period.

RESULTS:

The patients had lower serum free and total thyroxine concentrations and higher serum total triiodothyronine concentrations after treatment with thyroxine plus triiodothyronine than after thyroxine alone, whereas the serum thyrotropin concentrations were similar after both treatments. Among 17 scores on tests of cognitive performance and assessments of mood, 6 were better or closer to normal after treatment with thyroxine plus triiodothyronine. Similarly, among 15 visual-analogue scales used to indicate mood and physical status, the results for 10 were significantly better after treatment with thyroxine plus triiodothyronine. The pulse rate and serum sex hormone-binding globulin concentrations were slightly higher after treatment with thyroxine plus triiodothyronine, but blood pressure, serum lipid concentrations, and the results of neurophysiologic tests were similar after the two treatments.

CONCLUSIONS:

In patients with hypothyroidism, partial substitution of triiodothyronine for thyroxine may improve mood and neuropsychological function; this finding suggests a specific effect of the triiodothyronine normally secreted by the thyroid gland

Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism.
Smith RN, Taylor SA, Massey JC.

Abstract

A -double-blind crossover trial of a combined preparation of triiodothyronine and thyroxine (1:4 ratio) compared with thyroxine alone was conducted with 99 patients previously stabilized on. thyroxine as treatment for hypothyroidism. Four patients were excluded during the trial and eight afterwards owing to gross deficiencies in taking the tablets. Of the remaining 87 patients 42 (48%) had no -preference for either medication, 29 (33%) preferred thyroxine alone, and 16 (18%) the combination. A high incidence of unpleasant symptoms was experienced during the two months' treatment with the combined preparation. The serum protein-bound iodine levels were lowered (mean reduction 1.8 mug./100 ml.) on the combination, but the labelled T(3)-resin sponge uptake values were not altered and remained in the normal range. on both treatments

1. Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease.

Bunevicius R[1], Jakuboniene N, Jurkevicius R, Cernicat J, Lasas L, Prange AJ Jr.

1.1.1 Author information
1.1.2 Erratum in

- Endocrine. 2014 Feb;45(1):161. Jakubonien, Neli [corrected to Jakuboniene, Neli].

1.1.3 Abstract

It was recently demonstrated that treatment with levorotatory thyroxine (T4) plus triiodothyronine (T3) compared with treatment with T4 alone improves psychologic functioning in hypothyroid patients with thyroid cancer or autoimmune thyroiditis. In the present double-blind crossover study, we again compared the effects of combined thyroid replacement vs monotherapy on psychologic function, endocrine function, cardiovascular function, and body composition. The patients were women who were hypothyroid after thyroidectomy for Graves' disease. The substitution of 10 microg of T3 for 50 microg of T4 caused a statistically significant decrease in free T4 concentration but no significant change in T3 or thyroid-stimulating hormone concentration. Symptoms of hypothyroidism and of hyperthyroidism tended to decrease on a standard symptom scale after combined treatment. With combined hormone replacement, mental state tended to improve on some mood scales but not on cognitive tests. We found alterations in left ventricular diastolic function but no change in body composition after the combined treatment regimen. These preliminary findings in a small group of patients with Graves' disease are consistent with earlier findings that thyroid replacement with T4-T3 combination improves mental functioning

2. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial.

Clyde PW[1], Harari AE, Getka EJ, Shakir KM.

CONTEXT:

Standard therapy for patients with primary hypothyroidism is replacement with synthetic thyroxine, which undergoes peripheral conversion to triiodothyronine, the active form of thyroid hormone. Within the lay population and in some medical communities, there is a perception that adding synthetic triiodothyronine, or liothyronine, to levothyroxine improves the symptoms of hypothyroidism despite insufficient evidence to support this practice.

OBJECTIVE:

To evaluate the benefits of treating primary hypothyroidism with levothyroxine plus liothyronine combination therapy vs levothyroxine monotherapy.

DESIGN, SETTING, AND PATIENTS:

Randomized, double-blind, placebo-controlled trial conducted from May 2000 to February 2002 at a military treatment facility that serves active duty and retired military personnel and their family members. The trial included a total of 46 patients aged 24 to 65 years with at least a 6-month history of treatment with levothyroxine for primary hypothyroidism.

INTERVENTION:

Patients received either their usual dose of levothyroxine (n = 23) or combination therapy (n = 23), in which their usual levothyroxine dose was reduced by 50 micro g/d and substituted with liothyronine, 7.5 micro g, taken twice daily for 4 months.

MAIN OUTCOME MEASURES:

Scores on a hypothyroid-specific health-related quality-of-life (HRQL) questionnaire, body weight, serum lipid levels, and 13 neuropsychological tests measured before and after treatment.

RESULTS:

Serum thyrotropin levels remained similar and within the normal range in both treatment groups from baseline to 4 months. Body weight and serum lipid levels did not change. The HRQL questionnaire scores improved significantly in both the control group (23%; P<.001) and the combination therapy group (12%; P =.02), but these changes were statistically similar (P =.54). In 12 of 13 neuropsychological tests, outcomes between groups were not significantly different; the 1 remaining test (Grooved Peg Board) showed better performance in the control group.

CONCLUSION:

Compared with levothyroxine alone, treatment of primary hypothyroidism with combination levothyroxine plus liothyronine demonstrated no beneficial changes in body weight, serum lipid levels, hypothyroid symptoms as measured by a HRQL questionnaire, and standard measures of cognitive performance

3. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism.

Walsh JP[1], Shiels L, Lim EM, Bhagat CI, Ward LC, Stuckey BG, Dhaliwal SS, Chew GT, Bhagat MC, Cussons AJ.

T(4) is standard treatment for hypothyroidism. A recent study reported that combined T(4)/liothyronine (T(3)) treatment improved well-being and cognitive function compared with T(4) alone. We conducted a double-blind, randomized, controlled trial with a crossover design in 110 patients (101 completers) with primary hypothyroidism in which liothyronine 10 micro g was substituted for 50 micro g of the patients' usual T(4) dose. No significant ($P < 0.05$) difference between T(4) and combined T(4)/T(3) treatment was demonstrated on cognitive function, quality of life scores, Thyroid Symptom Questionnaire scores, subjective satisfaction with treatment, or eight of 10 visual analog scales assessing symptoms. For the General Health Questionnaire-28 and visual analog scales assessing anxiety and nausea, scores were significantly ($P < 0.05$) worse for combined treatment than for T(4) alone. Serum TSH was lower during T(4) treatment than during combined T(4)/T(3) treatment (mean +/- SEM, 1.5 +/- 0.2 vs. 3.1 +/- 0.2 mU/liter; $P < 0.001$), a potentially confounding factor; however, subgroup analysis of subjects with comparable serum TSH concentrations during each treatment showed no benefit from combined treatment compared with T(4) alone. We conclude that in the doses used in this study, combined T(4)/T(3) treatment does not improve well-being, cognitive function, or quality of life compared with T(4) alone.

4. Does a combination regimen of thyroxine (T4) and 3,5,3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial.

Sawka AM[1], Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT.

Some hypothyroid patients receiving levothyroxine replacement therapy complain of depressive symptoms despite normal TSH measurements. It is not known whether adding T(3) can reverse such symptoms. We randomized 40 individuals with depressive symptoms who were taking a stable dose of levothyroxine for treatment of hypothyroidism (excluding those who underwent thyroidectomy or radioactive iodine ablation of the thyroid) to receive T(4) plus placebo or the combination of T(4) plus T(3) in a double-blind manner for 15 wk. Participants receiving combination therapy had their prestudy dose of T(4) dropped by 50%, and T(3) was started at a dose of 12.5 micro g, twice daily. T(4) and T(3) doses were adjusted to keep goal TSH concentrations within the normal range. Compared with the group taking T(4) alone, the group taking both T(4) plus T(3) did not report any improvement in self-rated mood and well-being scores that included all subscales of the Symptom Check-List-90, the Comprehensive Epidemiological Screen for Depression, and the Multiple Outcome Study ($P > 0.05$ for all indexes). In conclusion, the current data do not support the routine use of combined T(3) and T(4) therapy in hypothyroid patients with depressive symptoms

5. Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14 : 1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism.

Siegmund W[1], Spieker K, Weike AI, Giessmann T, Modess C, Dabers T, Kirsch G, Sänger E, Engel G, Hamm AO, Nauck M, Meng W.

OBJECTIVES:

There is evidence from recent controlled clinical studies that replacement therapy of hypothyroidism with T4 in combination with a small amount of T3 may improve the well-being of the patients. As the issue is still the subject of controversial discussion, our study was assigned to confirm the superiority of a physiological combination of thyroid hormones (absorbed molar ratio 14 : 1) over T4 alone with regard to mood states and cognitive functioning.

DESIGN AND PATIENTS:

After a run-in period with the T4 study medication for 4 weeks, a controlled, randomized, double-blind, two-period (each 12 weeks), cross-over study without washout between the treatment periods was performed in 23 hypothyroid patients (three males, 20 females, age 23-69 years, 21 subjects after surgery/radioiodine, two with autoimmune thyroiditis) to compare the effects of the previous individual T4 dose (100-175 micro g) with a treatment in which 5% of the respective T4 dose was substituted by T3.

MEASUREMENTS:

Standard hormonal characteristics and standardized psychological tests to quantify mood and cognitive performance were measured after the run-in period and at the end of each treatment period. In 12 subjects, the concentration-time profiles of fT3 and fT4 were compared after the last administration of the respective study medication. TSH, fT3 and fT4 were measured with immunological assays.

CLINICAL RESULTS:

Replacement therapy with T4 and T4/T3 was not different in all steady-state hormonal, metabolic and cardiovascular characteristics except for TSH, which was more suppressed after T4/T3. The efficacy of replacement therapy with the T4/T3 combination was not different from the T4 monotherapy with regard to all psychological test scores describing mood and cognitive functioning of the patients. Mood was even significantly impaired by the T4/T3 combination in eight subjects, with TSH < 0.02 mU/l, compared to patients with normal TSH (Beck Depression Inventory: 8.25 +/- 5.01 vs. 4.07 +/- 5.60, P = 0.026). PHARMACOKINETIC RESULTS: The area under the concentration-time curve (AUC(0-8h)) of fT3 was significantly higher after T4/T3 compared to the T4 monotherapy (42.8 +/- 9.03 pmol x h/l vs. 36.3 +/- 8.50 pmol x h/l, P < 0.05) and was significantly correlated to serum TSH (r(s) = -0.609, P < 0.05). After T4/T3, patients with a history of Graves' disease or autoimmune thyroiditis had significantly higher serum trough levels of fT3 whereas the fT4 concentrations were significantly lower in patients with a nonautoimmune background.

CONCLUSION:

Replacement therapy of hypothyroidism with T4 plus T3 does not improve mood and cognitive performance compared to the standard T4 monotherapy. There is even a higher risk of signs of subclinical hyperthyroidism associated with impaired well-being of the patients, which is clearly caused by significant fluctuations in the steady-state fT3 serum concentrations

6. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone.

Escobar-Morreale HF[1], Botella-Carretero JI, Gómez-Bueno M, Galán JM, Barrios V, Sancho J.

BACKGROUND:

Substituting part of the dose of l-thyroxine with small but supraphysiologic doses of liothyronine in hypothyroid patients has yielded conflicting results.

OBJECTIVE:

To evaluate combinations of L-thyroxine plus liothyronine in hypothyroid patients that match the proportions present in normal secretions of the human thyroid gland.

DESIGN:

Randomized, double-blind, crossover trial.

SETTING:

Academic research hospital.

PARTICIPANTS:

28 women with overt primary hypothyroidism.

INTERVENTION:

Crossover trial comparing treatment with l-thyroxine, 100 microg/d (standard treatment), versus treatment with L-thyroxine, 75 microg/d, plus liothyronine, 5 microg/d (combination treatment), for 8-week periods. All patients also received L-thyroxine, 87.5 microg/d, plus liothyronine, 7.5 microg/d (add-on combination treatment), for a final 8-week add-on period.

MEASUREMENTS:

Primary outcomes included serum thyroid hormone levels, results of quality-of-life and psychometric tests, and patients' preference. Multiple biological thyroid hormone end points were studied as secondary outcomes.

RESULTS:

Compared with standard treatment, combination treatment led to lower free thyroxine levels (decrease, 3.9 pmol/L [95% CI, 2.5 to 5.3 pmol/L]), slightly higher serum levels of thyroid-stimulating hormone (increase, 0.62 mU/L [CI, 0.01 to 1.23 mU/L]), and unchanged free triiodothyronine levels. No improvement was observed in the other primary and secondary end points after combination treatment, with the exception of the Digit Span Test, in which the mean backward score and the mean total score increased slightly (0.6 digit [CI, 0.1 to 1.0 digit] and 0.8 digit [CI, 0.2 to 1.4 digits], respectively). The add-on combination treatment resulted in overreplacement. Levels of thyroid-stimulating hormone decreased by 0.85 mU/L

(CI, 0.27 to 1.43 mU/L) and serum free triiodothyronine levels increased by 0.8 pmol/L (CI, 0.1 to 1.5 pmol/L) compared with standard treatment; 10 patients had levels of thyroid-stimulating hormone that were below the normal range. Twelve patients preferred combination treatment, 6 patients preferred the add-on combination treatment, 2 patients preferred standard treatment, and 6 patients had no preference (P = 0.015).

LIMITATIONS:

Treatment with L-thyroxine, 87.5 microg/d, plus liothyronine, 7.5 microg/d, was an add-on regimen and was not randomized.

CONCLUSIONS:

Physiologic combinations of L-thyroxine plus liothyronine do not offer any objective advantage over l-thyroxine alone, yet patients prefer combination treatment.

Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial.

Appelhof BC[1], Fliers E, Wekking EM, Schene AH, Huyser J, Tijssen JG, Endert E, van Weert HC, Wiersinga WM.

Author information

Abstract

Controversy remains about the value of combined treatment with levothyroxine (LT4) and liothyronine (LT3), compared with LT4 alone in primary hypothyroidism. We compared combined treatment with LT4 and LT3 in a ratio of 5:1 or 10:1 with LT4 monotherapy. We conducted a double-blind, randomized, controlled trial in 141 patients (18-70 yr old) with primary autoimmune hypothyroidism, recruited via general practitioners. Inclusion criteria included: LT4 treatment for 6 months or more, a stable dose for 6 wk or more, and serum TSH levels between 0.11 and 4.0 microU/ml (mU/liter). Randomization groups were: 1) continuation of LT4 (n = 48); 2) LT4/LT3, ratio 10:1 (n = 46); and 3) LT4/LT3, ratio 5:1 (n = 47). Subjective preference of study medication after 15 wk, compared with usual LT4, was the primary outcome measure. Secondary outcomes included scores on questionnaires on mood, fatigue, psychological symptoms, and a substantial set of neurocognitive tests. Study medication was preferred to usual treatment by 29.2, 41.3, and 52.2% in the LT4, 10:1 ratio, and 5:1 ratio groups, respectively (chi2 test for trend, P = 0.024). This linear trend was not substantiated by results on any of the secondary outcome measures: scores on questionnaires and neurocognitive tests consistently ameliorated, but the amelioration was not different among the treatment groups. Median end point serum TSH was 0.64 microU/ml (mU/liter), 0.35 microU/ml (mU/liter), and 0.07 microU/ml (mU/liter), respectively [ANOVA on ln(TSH) for linear trend, P < 0.01]. Mean body weight change was +0.1, -0.5, and -1.7 kg, respectively (ANOVA for trend, P = 0.01). Decrease in weight, but not decrease in serum TSH was correlated with increased satisfaction with study medication. Of the patients who preferred combined LT4/LT3 therapy, 44% had serum TSH less than 0.11 microU/ml (mU/liter). Patients preferred combined LT4/LT3 therapy to usual LT4 therapy, but changes in mood, fatigue, well-being, and neurocognitive functions could not satisfactorily explain why the primary outcome was in favor of LT4/LT3 combination therapy. Decrease in body weight was associated with satisfaction with study medication

7. Substitution of liothyronine at a 1:5 ratio for a portion of levothyroxine: effect on fatigue, symptoms of depression, and working memory versus treatment with levothyroxine alone.

Rodriguez T[1], Lavis VR, Meininger JC, Kapadia AS, Stafford LF.

OBJECTIVE:

To attempt to confirm a previous report of superior effectiveness of using two thyroid hormones rather than one hormone to treat hypothyroidism.

METHODS:

This trial attempted to replicate prior findings, which suggested that substituting 12.5 microg of liothyronine (LT(3)) for 50 microg of levothyroxine (LT(4)) might improve mood, cognition, and physical symptoms in patients with primary hypothyroidism. Additionally, this trial aimed to extend the previous findings to fatigue and to assess for differential effects in subjects with low fatigue and high fatigue at baseline. A randomized, double-blind, two-period, crossover design was used. At an endocrinology and diabetes clinic, 30 adult subjects with primary hypothyroidism stabilized on LT(4) were recruited. Patients randomly assigned to treatment sequence 1 received their standard LT(4) dose in one capsule and placebo in another. Patients assigned to sequence 2 received their usual LT(4) dose minus 50 microg in one capsule and 10 microg of LT(3) in the other. At the end of the first 6 weeks, subjects were crossed over to receive the other treatment. Carryover and treatment effects were assessed by t tests.

RESULTS:

Of the 30 enrolled study subjects, 27 completed the trial. The mean LT(4) dose was 121 +/- 26 microg/day at baseline. No significant differences in fatigue and symptoms of depression were found between treatments. Measures of working memory were unchanged. During substitution treatment, the free thyroxine index was reduced by 0.7 ($P<0.001$), total serum thyroxine was reduced by 3.0 microg/dL ($P<0.001$), and total serum triiodothyronine was increased by 20.5 ng/dL ($P = 0.004$).

CONCLUSION:

With regard to the outcomes measured, substitution of LT(3) at a 1:5 ratio for a portion of baseline LT(4) yielded no better results than did treatment with the original dose of LT(4) alone

8. Partial substitution of thyroxine (T4) with tri-iodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial.

Saravanan P[1], Simmons DJ, Greenwood R, Peters TJ, Dayan CM.

Conflicting results have recently been published about the benefits of combined T(4) and T(3) in treating hypothyroid patients. However, these studies may have been underpowered to detect differences in psychological well-being specifically related to T(4) replacement. We conducted a large, double-blind, randomized controlled trial of partial substitution of 50 microg T(4) by 10 microg T(3) vs. the original dose of T(4) in 697 hypothyroid patients. Thyroid function showed a rise in TSH (132%), a fall in free T(4) (35%, P < 0.001), and unchanged basal free T(3) levels (P = 0.92). At 3 months, there was a large (39%) placebo effect improvement in psychiatric caseness defined by the General Health Questionnaire (GHQ) 12 score in the control group compared with baseline, and this was sustained at 12 months. Differences vs. the intervention (T(3)) group were more modest with improvements in GHQ caseness (odds ratio, 0.61; 95% confidence interval, 0.42, 0.90; P = 0.01) and Hospital Anxiety and Depression questionnaire-anxiety scores at 3 months (P < 0.03) but not GHQ Likert scores, Hospital Anxiety and Depression questionnaire-depression, thyroid symptoms, or visual analog scales of mood and the initial differences were lost at 12 months. These results may be consistent with a subgroup of patients showing transient improvement after partial substitution with T(3) but do not provide conclusive evidence of specific benefit from partial substitution of T(4) by T(3) in patients on T(4) replacement. They also emphasize the large and sustained placebo effect that can follow changes in thyroid hormone administration

Effect of combination therapy with thyroxine (T4) and 3,5,3'-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study.

Nygaard B[1], Jensen EW, Kvetny J, Jarløv A, Faber J.

Author information

Abstract

BACKGROUND:

Treatment of hypothyroidism with 3,5,3'-triiodothyronine (T(3)) is controversial. A recent meta-analysis concludes that no evidence is present in favour of using T(3). However, the analysis included a mixture of different patient groups and dose-regimens.

OBJECTIVE:

To compare the effect of combination therapy with thyroxine (T(4)) and T(3) versus T(4) monotherapy in patients with hypothyroidism on stable T(4) substitution. Study design Double-blind, randomised cross-over. Fifty micrograms of the usual T(4) dose was replaced with either 20 microg T(3) or 50 microg T(4) for 12 weeks, followed by cross-over for another 12 weeks. The T(4) dose was regulated if needed, intending unaltered serum TSH levels. Evaluation Tests for quality of life (QOL) and depression (SF-36, Beck Depression Inventory, and SCL-90-R) at baseline and after both treatment periods. Inclusion criteria Serum TSH between 0.1 and 5.0 mU/l on unaltered T(4) substitution for 6 months.

RESULTS:

A total of 59 patients (55 women); median age 46 years. When comparing scores of QOL and depression on T(4) monotherapy versus T(4)/T(3) combination therapy, significant differences were seen in 7 out of 11 scores, indicating a positive effect related to the combination therapy. Forty-nine percent preferred the combination and 15% monotherapy (P=0.002). Serum TSH remained unaltered between the groups as intended.

CONCLUSION:

In a study design, where morning TSH levels were unaltered between groups combination therapy, (treated with T(3) 20 microg once daily) was superior to monotherapy by evaluating several QOL, depression and anxiety rating scales as well as patients own preference

Efficacy of combined levothyroxine and liothyronine as compared with levothyroxine monotherapy in primary hypothyroidism: a randomized controlled trial.

Valizadeh M[1], Seyyed-Majidi MR, Hajibeigloo H, Momtazi S, Musavinasab N, Hayatbakhsh MR.

Author information

Abstract

OBJECTIVES:

To examine the efficacy of combination therapy with levothyroxine and liothyronine in improvement of general health, psychological problems, and metabolic status in primary hypothyroidism.

METHODS:

Seventy-one patients diagnosed with primary hypothyroidism were randomly allocated into two study groups: the first group received usual dose of levothyroxine and the second group received combination of levothyroxine and liothyronine for at least 4 months. The main outcomes were psychosocial problems (Goldberg's General Health Questionnaire, GHQ-28), bodyweight, heart rate, blood pressure, and serum lipid levels.

RESULTS:

In both groups serum thyroid-stimulating hormone levels remained unchanged compared with baseline. Psychosocial scores, body weight, heart rate, blood pressure, and lipid profile in the two groups remained constant. The only exception was a small but significant reduction in anxiety/insomnia in combined treatment group as compared with monotherapy.

CONCLUSIONS:

The data do not support the hypothesis that combined therapy improves the well-being and general health of patients

Combined therapy with L-thyroxine and L-triiodothyronine compared to L-thyroxine alone in the treatment of primary hypothyroidism.

Fadeyev VV[1], Morgunova TB, Melnichenko GA, Dedov II.

Author information

Abstract

OBJECTIVE:

The objective of this study was to compare various parameters in patients with hypothyroidism receiving either monotherapy with L-thyroxine (L-T4) or combination therapy with L-T4 and L-triiodothyronine (L-T3).

DESIGN:

We conducted a randomized, controlled trial in 36 premenopausal women with hypothyroidism. The patients were divided into two groups: Group A (n=20) received only L-T4, while Group B received the combination L-T4 and L-T3. The treatment period lasted for 6 months.

RESULTS:

At baseline, the various parameters examined did not differ in the two groups. No significant difference between monotherapy and combined therapy was demonstrated on TSH level, ECG monitoring, densitometry, or thyroid symptoms score. The lipid profile was better during combined treatment compared to L-T4 alone; in Group A during treatment with L-T4 the levels of cholesterol and low density lipoprotein (LDL) cholesterol were unchanged, while in group B total cholesterol and LDL decreased ($p<0.05$). The changes in osteocalcin levels did not differ in the two groups, whereas the levels of urine deoxypyridinoline at the end of therapy were higher in the group with combination therapy, compared to monotherapy.

CONCLUSION:

Compared with L-T4 alone, replacement therapy with the combination of L-T4+L-T3 shows favourable changes in serum lipid profile, but higher activation of bone resorption

FINDINGS FROM META-ANALYSES OF LIOTHYRONINE

REVIEW: Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine.

Escobar-Morreale HF[1], Botella-Carretero JI, Escobar del Rey F, Morreale de Escobar G.

Author information

Abstract

CONTEXT:

Combined infusion of levothyroxine plus liothyronine, as opposed to levothyroxine alone, is the only way of restoring the concentrations of circulating TSH, T4, and T3 as well as those of both T4 and T3 in all tissues of thyroidectomized rats. Considering the substantial differences in thyroid hormone secretion, transport, and metabolism between rats and humans, whether or not combined levothyroxine plus liothyronine replacement therapy has advantages over treatment with levothyroxine alone in hypothyroid patients is still questioned.

EVIDENCE ACQUISITION:

We conducted a systematic review of all the published controlled studies comparing treatment with levothyroxine alone with combinations of levothyroxine plus liothyronine in hypothyroid patients, identified through the Entrez-PubMed search engine.

EVIDENCE SYNTHESIS:

Nine controlled clinical trials were identified that compared treatment with levothyroxine alone and treatment with combinations of levothyroxine plus liothyronine and included a sufficient number of adult hypothyroid patients to yield meaningful results. In only one study did the combined therapy appear to have beneficial effects on the mood, quality of life, and psychometric performance of the patients over levothyroxine alone. These results have not been confirmed by later studies using either T3 substitution protocols or approaches with fixed combinations of levothyroxine plus liothyronine, including those based on the physiological proportion in which T3 and T4 are secreted by the human thyroid. However, in some of these studies the patients preferred levothyroxine plus liothyronine combinations, for reasons not explained by changes in the psychological and psychometric tests employed. Yet patients' preference should be balanced against the possibility of adverse events resulting from the addition of liothyronine to levothyroxine, even in the small doses used in these studies.

CONCLUSIONS:

Until clear advantages of levothyroxine plus liothyronine are demonstrated, the administration of levothyroxine alone should remain the treatment of choice for replacement therapy of hypothyroidism.

Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials.

Grozinsky-Glasberg S[1], Fraser A, Nahshoni E, Weizman A, Leibovici L.

Author information

Abstract

CONTEXT:

In some patients symptoms of hypothyroidism persist despite therapy with T(4).

OBJECTIVE:

The objective of the study was to compare the effectiveness of T(4)-T(3) combination vs. T(4) monotherapy for the treatment of clinical hypothyroidism in adults.

DATA SOURCES:

PubMed, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched in September 2005. References of all included trials were scanned for additional studies. We put no restrictions on language, year of publication, or publication status.

STUDY SELECTION:

All randomized trials that compared the effectiveness of T(4)-T(3) combination vs. T(4) monotherapy for the treatment of clinical hypothyroidism in adults were included.

DATA EXTRACTION:

The data were extracted by two independent reviewers.

DATA SYNTHESIS:

We included 11 studies, in which 1216 patients were randomized. No difference was found in the effectiveness of combination vs. monotherapy in any of the following symptoms: bodily pain [standardized mean difference (SMD) 0.00, 95% confidence interval (CI) -0.34, 0.35], depression (SMD 0.07, 95% CI -0.20, 0.34), anxiety (SMD 0.00, 95% CI -0.12, 0.11), fatigue (SMD -0.12, 95% CI -0.33, 0.09), quality of life (SMD 0.03, 95% CI -0.09, 0.15), body weight, total serum cholesterol, triglyceride levels, low-density lipoprotein, and high-density lipoprotein. Adverse events did not differ between regimens.

CONCLUSIONS:

T(4) monotherapy should remain the treatment of choice for clinical hypothyroidism

Treatment of clinical hypothyroidism with thyroxine and triiodothyronine: a literature review and metaanalysis.

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Author information

Abstract

Thyroxine is the standard replacement therapy for patients with clinical hypothyroidism. However, there has been recent interest in examining the potential advantages of combined thyroxine and triiodothyronine treatment for the treatment of hypothyroidism. The authors review the nine studies to-date and conclude that the variability and limitations in study design make definitive and clinically useful recommendations difficult. They therefore conducted a metaanalysis of the nine controlled studies examining the impact of combined thyroxine-plus-triiodothyronine versus thyroxine alone, with measures of psychiatric symptoms as the primary outcome. Their analysis reveals no significant difference in treatment effect on psychiatric symptoms in the nine controlled studies to date

Thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism.

Ma C[1], Xie J, Huang X, Wang G, Wang Y, Wang X, Zuo S.

Author information

Abstract

Standard therapy for patients with hypothyroidism is replacement with synthetic thyroxine (T4). However, thyroxine plus triiodothyronine (T3) replacement therapy resulted in marked improvements in several items of the Profile of Mood States and in a few indices of psychometric function and quality of life. The adequacy of thyroxine alone versus thyroxine plus triiodothyronine to treat hypothyroidism has yielded conflicting results. Therefore, we conducted a systematic review of all included published, randomized controlled trials to evaluate the effects of thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism. We electronically searched Medline, Embase, the Cochrane Library, and China National Infrastructure. We also manually searched the Chinese Journal of Isotopes, Radiologia pratica, and the Chinese Journal of Endocrinology and Metabolism. A total of 10 randomized, double-blind trials (six crossovers, four parallel trials) were identified. Pooled analyses were suggestive of a statistically significant increase of free and total triiodothyronine, significant decrease of serum-free and total thyroxine in patients treated with thyroxine plus triiodothyronine, weighted mean difference (WMD) 0.03, -31.25, 2.19, 3.00; 95% confidence interval (CI) -0.14 to 0.20, -47.04 to -15.47, 0.46-3.92, 1.64-4.36, respectively. Thyroxin alone indicated significant benefits for psychological or physical well-being in terms of the General Health Questionnaire-28 (WMD: -2.90; 95% CI: -3.18 to -2.63), general health (WMD: -0.38; 95% CI: -0.71 to -0.05), physical component summary (WMD: 0.7; 95% CI: 0.53-0.87), and mental component summary (WMD: 0.58; 95% CI: 0.25-0.75); physical functioning (WMD: 1.60; 95% CI: 1.29-1.90), role-physical test (WMD: 3.60; 95% CI: 2.66-4.54), bodily pain (WMD: 2.50; 95% CI: 2.11-2.88), role-emotional (WMD: 2.08; 95% CI: 1.17-2.99), mental health (WMD: 1.30; 95% CI: 0.97-1.64) in items of the Short Form-36 Health Survey; general well-being in items of the Thyroid Symptom Questionnaire (WMD: -1.90; 95% CI: -2.48 to -1.32); better performance in the Letter Number Sequencing-working memory test in items of cognitive performance scores (WMD: 1.10; 95% CI: 0.08-2.13), significant treatment effect for blurred vision, aches, and pain (WMD: -4.66, -0.80; 95% CI: -5.339 to -4.00, -1.34 to -0.26, respectively). However, T4 plus T3 replacement improved cognitive performance (WMD: -0.49; 95% CI: -0.90 to -0.08). No significant statistical differences were found in biochemical variables, mood states clinical variables, adverse effects, and drop-out. In subgroup analysis, two included studies examined the relationship between mental improvement and causes of hypothyroidism, autoimmune, and nonautoimmune hypothyroidism, respectively. T4 alone suggested significantly higher total T4 (autoimmune and nonautoimmune thyroid, WMD: 4.5, 3.7; 95% CI: 2.24-6.76, 1.66-5.74, respectively), and significantly decreased thyroid-stimulating hormone (WMD: -0.05; 95% CI: -0.09 to -0.01). Statistically significant improvement occurred in pairs correctly recalled in the Digit Symbol Test for T4 plus T3 replacement (WMD: -1.60; 95% CI: -2.97 to -0.23) for nonautoimmune thyroid. In conclusion, on the basis of data from recent studies, we conclude that combined T4 and T3 treatment does not improve well-being, cognitive function, or quality of life compared with T4 alone. T4 alone may be beneficial in improving psychological or physical well-being. According to the current evidence, T4 alone replacement may remain the drug of choice for hypothyroid patients

ANNEX D

BTA POSITION STATEMENT ON MANAGEMENT OF PRIMARY HYPOTHYRIODISM

http://www.british-thyroid-association.org/news/BTA_Hypothyroidism_Statement.pdf