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Research Article

Activity of a Combination of Physiological Modulators in Limiting Side Effects in Patients Suffering from Primary Hypothyroidism during Levothyroxine Treatment

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Abstract

Design: The combination of Physiological Modulators (CPMs) was shown to decrease the occurrence of side effects in the initial phase of treatment with LT_4.

Objective: The aim was to determine whether this action occurred also during stable chronic treatment with LT_4.

Methods: Double-blind randomized trial in 48 outpatients (two groups) of patients under treatment with LT_4 at doses ranging from 50 to 125µg/day from at least one year. Patients were treated respectively with placebo (Group A) and CPMs (Group B) for 30 days. T3, T4, TSH, plasma hydroperoxides (Carr. U.) and hs-CRP were measured. Side effects (anxiety/restlessness, sweating, palpitations and headache) and discomfort were assessed daily using a questionnaire.

Results: Hormone balance (T3, T4 and TSH) was adequate in both groups. After 30 days of treatment, a significant decrease (t-test $p<0.001$) in hydroperoxides levels from 385 ± 21.0 to 317 ± 37.7 Carr U together with a decrease in hs-CRP from 4.1 ± 1.11 to 3.6± 0.92 mg/L was observed only in the group treated with CPMs. In the group treated with placebo no significant reduction was shown. The incidence of side effects and the number of days with daily discomfort were significantly reduced in the group treated with CPMs. Between 79 % and 90% showed a decrease in side effects and daily discomfort.

Conclusions: Use of CPMs significantly reduces the incidence of side effects and daily discomfort during chronic treatment with LT_4.

Keywords: T4; T3; TSH; Hydro peroxides; hs-CRP; LT_4 side effects

Introduction

The report on Adverse Events Reporting in Patients Treated with Levothyroxine (LT_4) [1] indicates that 23 % of the cases are affected by side effects due exclusively to LT_4 treatment.

In a previous trial [2], it was observed that in the initial stage of treatment of the primary hypothyroidism with LT_4, side effects can arise, although not serious in nature, and cause moderate daily discomfort. This discomfort was mainly due to symptoms such as anxiety/restlessness, sweating, palpitations and headache that were concomitant with the increase in plasma hydroperoxides (an index of oxidative stress or OS) and to the rise in serum levels of hs-CRP.

This condition leads to limitations in working activity, but could be significantly reduced using a combination of Physiological Modulators [CPMs] consisting of vitamin E, procyanidins, astaxanthin, lipoic acid and lycopene at low dosages [3].

Some of the side effects tend to fade away over time, both because the patient gets used to putting up with them and due to metabolic/psychological compensation that allows them to "live" with the disorders. What remains almost constant is the OS that can still become excessive on account of intercurrent diseases (hypertension, acute or chronic inflammation, diabetes, dyslipidemia or flu), habits (smoking and high oxidized fat diet) or use of drugs (among which contraceptives stand out as "stressors") [4].

These conditions can persist even with stable LT_4 treatment, which can be revealed through careful investigation (high hs-CPR, hydroperoxides or other OS markers), and this may still lead to a cohort of side effects. The most frequently reported among these are anxiety/restlessness, palpitations, sweating and a number of various other relatively rare symptoms, including muscle cramps, insomnia and gastric and dietary disorders.

Although all these symptoms are sporadic, they are unpredictable and unpleasant.

The use of CPMs with antioxidant and anti-inflammatory actions may curb this reactive condition, which may be defined as an "inflammatory redox" reaction. This condition may be triggered when LT_4 levels increase in proportion to daily absorption: there is inevitably a "wave peak" during the first 3-4 hours after it is taken.

In this double-blind trial against placebo, we aimed to determine the action of CPMs in reducing the frequency of side effects in

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subjects who had been receiving stable treatment with LT_4 for at least one year, regardless of the dose used.

Methods

Patients, inclusion and exclusion criteria

We analyzed 48 outpatients (18 M and 30 F) aged between 42 and 59, affected by primary hypothyroidism with mono or plurinodular goitre. All subjects had undergone biopsy to determine the state of their thyroid and were affected both with autoimmune and non-autoimmune primary hypothyroidism. They were administered hormone replacement therapy with LT_4 (Euthyrox®-Merck) at doses of between 50 and 125 μg/day and belonging to the same brand. The dosage of LT_4 was established by the Endocrinology departments where the patients belonged, and was stable for at least one year and the admitted. The trial was carried out with continuous treatment with the products under examination for a period of 30 days. The patients were divided into two groups (A and B) of 24 subjects each, balanced by sex, LT_4 dose, and length of LT_4 treatment. .

All the participants were informed about the scope of the trial and gave their informed consent.

The admission criteria included subjects with TSH values < 10 μU/dL and 22 < BMI < 30.

Female subjects in menopause were admitted only if they had been in menopause for at least two years without ongoing estrogen replacement therapy. Smoking was not among the exclusion criteria. Subjects with dyslipidemia were admitted only in case they had been under treatment for at least 6 months. Hypertension was not grounds for exclusion provided it had been suitably treated for not less than 6 months.

Subjects treated with fish oils were excluded as these can increase plasma hydroperoxides that add to any oxidative stress caused by LT_4.

Subjects undergoing weight-loss therapy or who are on a diet to lose weight and patients affected with any kind of tumor were excluded. Females taking oral contraceptives were not admitted since these products cause substantial OS [4].

Treatments

The protocol consisted of treatment with LT_4 at stable doses ranging from 50 to 125μg/day for at least one year, according to standard conditions (taken on an empty stomach in the morning, followed by breakfast after 30 minutes). The levothyroxine treatment was not changed for the whole 30-day period.

CPMs or placebo was prepared in type 0 capsules. Group A was treated with CPMs and group B with placebo. The two treatments were indistinguishable (four 10 capsule blister packs).

Up to 32 days of treatment were allowed if the thirtieth day fell on a Saturday. All treatments consisted of 1 capsule/day, taken just before going to bed at night. The capsules were administered in the evening in order to prevent the interference with the absorption of LT_4, which was administered in the morning.

Type of experiment

The study was a double-blind randomized trial.

Variables considered: We analyzed T4, T3 and TSH levels, levels of hydroperoxides (d-ROMs test in terms of Carr.U.) as an index of OS [5], and C-reactive protein (hs-CRP) as an index of systemic inflammation. Measurements were taken on two occasions: at baseline and after 30 (32) days of treatment with CPMs or placebo.

The occurrence of side effects of hormone replacement therapy that are considered most frequent, i.e. anxiety/restlessness, sweating, palpitation, headache and insomnia was also assessed. The subjects were given two fifteen-day diaries in which they had to note the above listed symptoms every day. There were also blank spaces for reporting "other symptoms".

All the subjects were instructed to record the occurrence or absence of the symptoms shown through a score ranging from 0 to 4, where 0 was no symptom and 4 was sufficiently serious to suggest the subject went to the center for tests and/or to change the dose of LT_4.

Each sheet covered a period of 15 days; therefore the frequency of each symptom could vary from 0 (never occurred) to 15 (occurred every day) and its total score was the sum of the two fifteen-day periods.

Besides the score, the patient was asked to mark "M" if the effect was observed before 2 pm, "S" if it was observed after 2 pm (the afternoon/evening period) and "MS" if the symptom was observed both in the morning and evening. These reports were used in order to establish whether there was a rough correlation between LT_4 levels and the observed effect. Since LT_4 was administered in the morning, a prevalence of "M" might suggest that the effects were related to the LT_4 "wave peak".

There were therefore two fifteen-day reports for all the variables taken into consideration for each subject.

The days during which the subject reported physical or mental discomfort that limited their performance of daily chores and/or working activities were also assessed and recorded so that this aspect could be compared with the side effects. These "days of discomfort" (dd) were assessed overall at the end of the 30-day treatment period.

If subjects suffered from any illnesses during the trial, their data were excluded from the final results.

Laboratory mthods: Serum T4 and T3 levels were measured using radio immunological methods (Diagnostic Products Corporation, Los Angeles). Serum T3 levels were measured using a radio immunological method (Magic T3 Radioimmunoassay, Bayer Corporation Diagnostic Division, Tarrytown NY). TSH levels were measured immunologically with the TTSH immulite 2000 (X) kit. OS was determined using the d-ROMs test, which measures plasma hydroperoxides in terms of Carr. U. (1 Carr. U. =0.08 mg H_2O_2/dL) [5] using the FRAS4 system (H&D srl -Parma-Italy). Triglycerides and total cholesterol levels were measured using an enzymatic method (Roche-Germany). hs-CRP levels were measured using an immunoturbidimetric method (Denka Seiken, Tokyo).

All the samples were taken in patients following overnight fasting and between 7:30 and 8:30 am before the LT_4 treatment. Four 5 mL blood samples were drawn from a brachial vein. To perform the d-ROMs test, the plasma was collected in the amount of 0.5 mL and kept at -80°C until the measurement was made.

Table 1: General characteristics of the two groups of subjects treated with LT_4, plus a physiological modulator (CPMs, group A) or a placebo (group B). Mean values ± SD of 23 patients/group.

Variables baseline	Groups		T-test/ Fisher test[a]
	A CPMs	B Placebo	
Number of cases dropout	24 1 M	24 1 M	
Age [years]	52 ± 6.2	50 ± 6.1	Ns
Sex	8 M; 15 F	8 M; 15 F	
Height [m]	1.67 ± 0.07	1.66 ± 0.06	Ns
Body weight [kg]	79 ± 5.3	77 ± 5.8	Ns
BMI [kg/m^2]	28.3 ± 1.14	28.0 ± 2.04	Ns
Total cholesterol [mg/dL]	246 ± 20.5	234 ± 18.9	Ns
Triglycerides [mg/dL]	225 ± 42.6	228 ± 29.9	Ns
d-ROMs [Carr. U.]	385 ± 21.0	376 ± 24.0	Ns
T4 [µg/dL]	14.3 ± 1.91	14.7 ± 1.59	Ns
T3 [ng/dL]	160.6 ± 18.59	162.1 ± 17.48	Ns
TSH [µU/dL]	6.1 ± 1.95	6.8 ± 2.91	Ns
hs-CRP [mg/L]	4.3 ± 0.82	4.1 ± 1.11	Ns
Hypertension	6/23	4/23	Ns[b]
Diabetes	3/23	4/23	Ns[b]
Smoking	11/23	13/23	Ns[a]
LT_4 doses			
50 µg	6/23	7/23	Ns[a]
75 µg	6/23	5/23	Ns[a]
100 µg	6/23	6/23	Ns[a]
125 µg	5/23	5/2	Ns[a]

*The parametric data were evaluated using the t-test for unpaired samples; [a]the non-parametric data were analyzed using the chi square test or [b]the exact Fisher test. Ns = not significant; $p < 0.05$.

Statistical analysis

Means and standard deviations (SD) were calculated for all data. Differences in the variables in the groups were analyzed using Student's t-test. The chi-square test (both with Yates correction and Fisher's exact) was used to assess differences in frequency. Fisher's exact test was used when the expected frequency was less than 5. The required sample size was calculated on the basis of hydroperoxide levels. Considering a type α error of 0.05, type 1-β error of 0.9, and mean differences of 1 SD, groups of 10 subjects were sufficient to achieve a power of greater than 0.9.

Compliance

Compliance with the protocol was measured by counting the remaining tablets returned by the patients (50-tablet blister packs of LT_4 at various doses) and remaining capsules (four 10-capsule blister packs).

Results

Two subjects (one in each group) did not complete the trial because they caught flu during the first few days. All the other subjects completed the trial and compliance was almost total (100%).

Table 1 shows the general characteristics of the two groups, which were equivalent for all the variables taken into account (t-test $p > 0.05$ for all comparisons between groups). Thyroid balancing was satisfactory at the doses of LT_4, which were similar in both groups.

The first observation to emerge was that the presence of OS at baseline was almost constant in all the subjects tested (normal values were < 300 Carr. U.) and the average values of hs-CRP in both groups far exceeded 4 mg/L, indicating the presence of an inflammatory state.

The mean values of the hormone balance variables achieved with LT_4 treatment were similar for both groups (Table 1 and Table 2) and could be considered satisfactory, both as regards the increases in levels of T4 and T3 and the reduction in levels of TSH.

Oxidative stress changed in the treated group (A), but not in the placebo group (B), and also hs-CRP levels were lowered significantly only in group A.

Side effects occurred in almost all subjects, but with very different daily frequencies in controls and patients treated with CPMs. It should however be noted that these effects were not very serious, only sporadically reaching magnitude 3 (very annoying), and the scores were generally lower in the treated group (data not shown).

Their overall occurrence during the 30-day period was significantly lower in group A than in group B (Table 2). The differences were already apparent at the test performed after 15 days (data not shown) and were stable during the following 15 days. For this reason, only the overall 30-day figure has been calculated for this report.

These differences proved to be statistically significant and different for all the side effects considered: decreases in frequency ranging from a minimum of 78% (sweating) to a maximum of 90% (daily discomfort) were recorded. It was also noted that most side effects were reported before 2 pm (M), with the exception of headache, which occurred more frequently after 2 pm (S), *i.e.* in the afternoon/evening. There were only a few cases of effects present throughout the entire day (MS).

Some symptoms, such as insomnia and cramps, were reported by a limited number of subjects and therefore were not analyzed in detail.

The days of discomfort showed a similar trend to that of the side effects. The mean value in group B was about 6 days (corresponding to approximately 17% of the observation period), while the mean value in group A was 0.6 days (corresponding to 2% of the observation period).

Discussion

The results of this trial indicate that it is possible to decrease the side effects that emerge during any stage of treatment with LT_4 and not just at the beginning [2,3].

The limits of this trial are related to some aspects of side effect monitoring: it is known that when patients are asked to report a particular symptom, they tend to overestimate its frequency, simply because they pay greater attention to reporting it. The similarity of the two fifteen-day reports shows that completion of the questionnaires was not significantly affected by their "novelty value" or by the need to find a side effect at all costs. They are therefore very likely to report the real events.

Table 2: Variables related to hypothyroidism balance and side effects following the daily administration of LT_4 together with a physiological modulator (CMPs, group A) or placebo (group B) for a period of 30 days.
Mean values ± SD of 23 subjects/group.

Variables at 30 days	Groups		T-test/ Chi-square test[a]
	A CPMs 1 capsule/day	B Placebo 1 capsule/day	
d-ROMs [Carr. U.]	317 ± 37.7	391 ±25.3	p < 0.01
T4 [µg/dL]	14.4 ± 1.99	14.8 ± 1.51	Ns
T3 [ng/dL]	159.5 ± 17.83	164.2 ± 18.81	Ns
TSH [µU/dL]	6.0 ± 1.93	6.5 ± 2.71	Ns
hs-CRP [mg/L]	3.6 ± 0.92	4.2 ± 1.02	p< 0.05
Anxiety/restlessness [I][b]	1.7 ± 1.13	8.0 ± 2.06	
M %	75	75	Ns[a]
S %	8	17	Ns[a]
MS %	17	25	Ns[a]
Sweating [I]	1.7 ± 0.95	7.8 ± 1.94	p<0.01
M %	75	75	Ns[a]
S %	8	17	Ns[a]
MS %	17	25	Ns[a]
Palpitations [I]	2.9 ± 1.86	16.4 ± 4.66	p< 0.01
M %	75	75	Ns[a]
S %	8	17	Ns[a]
MS %	17	25	Ns[a]
Headache [I]	1.2 ± 0.56	8.5 ± 2.21	p < 0.01
M %	33	33	Ns[a]
S %	58[d]	67[d]	Ns[a]
MS %	8	13	Ns[a]
Daily discomfort [g][c]	0.6 ± 0.58	5.8 ± 1.84	p < 0.01

The parametric data were evaluated using the t-test for unpaired samples; [a]the non-parametric data were analysed using the chi-square test. Ns = not significant; p <0.05; [b]Variable index from 0 to 30; [c] number of days out of 30; [d]the evening percentages (S) were significantly higher than the morning ones (M) according to chi-square test (p< 0.05).

Due to the risk linked to the monitoring of adverse events, the placebo and double-blind method were essential for correct assessment of the effects.

A further limitation of the study is related to the lack of a group of subject treated with CPMs and with no hypothyroidism in order to control their activity and side effects.

The results of the trial are interesting and may find application in clinical practice, particularly as regards OS and hs-CRP levels, which are more immune to any subjective "overstatement".

The increase of hydroperoxides levels was considered as one of the main causes of side effects and daily discomfort in patients treated with LT_4 [2,3] and for some authors also prognostic of mortality if patients suffered from cardiovascular disease [6].

The trial paints a picture of discomfort that is often underrated, not only by specialists, but also by general practitioners, who simply follow the patient for the concomitant diseases or just write LT_4 prescriptions.

Although the side effects produced, by stable treatment with LT_4 are unacknowledged or underrated and have never emerged as a serious problem, it is wrong to regard them as a "discomfort to put up with" and consider them as necessary events in order to obtain benefits.

This trial has shown that it is possible to achieve adequate hormone balance while preventing unnecessary discomfort and, at the same time, optimize the risk/benefit ratio.

The increase in hs-CRP shows that there is an underlying inflammatory condition in patients with hypothyroidism up on chronic treatment with LT_4, which may result in unpleasant symptoms related to poorly understand metabolic conditions. The fact that these symptoms are controllable by using specific physiological modulators confirms that they probably stem from a condition that may be defined as a reactive condition, which can be favourably altered when substances with anti-inflammatory and antioxidant action are used.

The side effects were mostly observed in rough correlation with LT_4 levels (during the "M" stage, *i.e.*, before 2 pm), when the circulating levels of LT_4 and tissue levels of T3 were on the rise, *i.e.* during the hours following replacement hormone administration.

Likewise, it is no surprise that these effects occur one day and are absent the next, only to reappear again unpredictably. This probably depends on conditions determined by eating habits, which necessarily vary, as well as the administration of other drugs in conjunction with the replacement therapy. Interferences between LT_4 treatment and drugs/foods are known, even though they are hard to decipher. It is therefore easy to observe level fluctuations, which may lead to critical conditions when the level increases, particularly during the hours following administration or, as in the case of headaches, which are delayed in comparison with the "peak wave level". We cannot exclude that certain side effects are caused by the decrease in LT_4 level, i.e. its "deprivation" after the peak.

In previous clinical trials, proanthocyanidins were observed to have a protective action in some diseases, such as chronic venous insufficiency [7], the complications of diabetes [8], and hemorrhoid treatment [9]. Taking these activities together, it may be generically defined as an antioxidant that also inhibits inflammatory reactions [10]. This has also been confirmed in the treatment of LT_4 side effects during the initial stage of its use, i.e. as the dose is under stabilization [3].

The clinical action of proanthocyanidins was therefore already sufficiently demonstrated and correlated with their pharmacological characteristics. A combination of proanthocyanidins with other physiological modulators (astaxanthin, lipoic acid, vitamin E, and lycopene) seems to be able to reduce oxidation and protect efficiently cell membranes [11,12,13,14,15]. These are highly affected by the damage caused by the production of reactive oxygen species (ROS). Vitamin E was shown to be effective in reducing dysfunction produced by hyperthyroidism [16].

Lipoic acid reduces the sensitivity of AGE (advanced glycation end-product) receptors. In other words, AGEs trip a monocyte reaction [17] and therefore a true aggression, which acts in a diffuse way on veins and nerves. These receptors are the beginning of the signal that causes "active" oxidation [18], which may also be defined

as an inflammatory redox reaction. Lipoic acid can behave as antioxidant both in the oxidized and reduced form and may chelate redox active metals [19]. Most important is its capability to reduce cystine to L-cysteine which supports the intracellular synthesis of GSH [20].

Lycopene is a carotenoid and it was considered to be part of the CPM formulation because hypothyroidism is characterized by an inflammatory status [21] that can end up with reduction of all the levels of all carotenoids [22]. Astaxanthin is also a carotenoid with a powerful antioxidant activity [23] with the characteristic to improve the microcirculation [24] which is compromised in hypothyroidism [25].

It should be borne in mind that hypothyroidism in itself clearly produces OS and therefore mitochondrial ROS leakage is already substantially present. In other words cells have trouble maintaining the energy levels they need and are worn down by oxidation. In this situation, a further mitochondrial stimulus produced by thyroid hormones may reduce the capacity to compensate for oxidation causing irreversible cell damage.

The physiological modulators provide essential support to control the OS and to reduce the inflammatory conditions. At the low dosages that are characteristics of the CPM formulation, they are completely safe and until now no side have been reported in the clinical studies that have been conducted. This is not the first time that different CPMs have shown some clinical activity as it has been found treating conditions such as cerebral OS [26], menopause [27] and OS generated by oral contraceptives [4].

Therefore, when treating hypothyroidism with LT_4, the use of a physiological modulator with anti-inflammatory and antioxidant actions overcome over the onset of the side effects produced by the rapid increase in the circulating and tissue levels of thyroid hormones.

Recently it has been shown that women under treatment with LT_4, because of overt hypothyroidism, may develop lung cancer that seems to be correlated with high LT_4 levels in lung tissue [28] that is generated by a condition of local OS. This last observation indicates that the fact that hormone supplementation in hypothyroidism can be life saving, more attention should be paid in order to avoid possible side effects due to LT_4 treatment.

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