Effects of Carnitine on Thyroid Hormone Action

SALVATORE BENVENGA,[a,b] ANTONINO AMATO,[c] MENOTTI CALVANI,[d] AND FRANCESCO TRIMARCHI[a]

[a]*Sezione di Endocrinologia, Dipartimento Clinico Sperimentale di Medicina e Farmacologia, University of Messina School of Medicine, 98125 Messina, Italy*

[b]*Programma Infradipartimentale di Endocrinologia Molecolare Clinica, Azienda Ospedaliera Universitaria Policlinico Gaetano Martino, 98125 Messina, Italy*

[c]*Sigma-Tau Research, Incorporated, Gaithersburg, Maryland 20877, USA*

[d]*Sigma-Tau S.p.A., 00040 Pomezia, Roma, Italy*

ABSTRACT: By experiments on cells (neurons, hepatocytes, and fibroblasts) that are targets for thyroid hormones and a randomized clinical trial on iatrogenic hyperthyroidism, we validated the concept that L-carnitine is a peripheral antagonist of thyroid hormone action. In particular, L-carnitine inhibits both triiodothyronine (T3) and thyroxine (T4) entry into the cell nuclei. This is relevant because thyroid hormone action is mainly mediated by specific nuclear receptors. In the randomized trial, we showed that 2 and 4 grams per day of oral L-carnitine are capable of reversing hyperthyroid symptoms (and biochemical changes in the hyperthyroid direction) as well as preventing (or minimizing) the appearance of hyperthyroid symptoms (or biochemical changes in the hyperthyroid direction). It is noteworthy that some biochemical parameters (thyrotropin and urine hydroxyproline) were refractory to the L-carnitine inhibition of thyroid hormone action, while osteocalcin changed in the hyperthyroid direction, but with a beneficial end result on bone. A very recent clinical observation proved the usefulness of L-carnitine in the most serious form of hyperthyroidism: thyroid storm. Since hyperthyroidism impoverishes the tissue deposits of carnitine, there is a rationale for using L-carnitine at least in certain clinical settings.

KEYWORDS: carnitine; thyroid hormone; T3; T4; hyperthyroid; bone mineral density (BMD)

INTRODUCTION

Basic and clinical studies appeared in the late 1950s and mid-1960s,[1–7] indicating that carnitine was capable of contrasting the effect of thyroid hormones (T3, T4) in

Address for correspondence: Prof. Salvatore Benvenga, Sezione di Endocrinologia, Dipartimento Clinico Sperimentale di Medicina e Farmacologia, University of Messina School of Medicine, and Programma Infradipartimentale di Endocrinologia Molecolare Clinica, Azienda Ospedaliera Universitaria Policlinico Gaetano Martino, 98125 Messina, Italy. Voice: +39-090-221-3840; fax: +39-090-221-3518.

s.benvenga@me.nettuno.it; sbenvenga@unime.it

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both animals and humans. Certain thyroid hormone–driven changes associated with the metamorphosis of tadpoles, as well as with the nitrogen balance or liver enzyme changes in rats, were antagonized.[1–3] For instance, T4 injected into the rats increased the activity (and presumably the mass) of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in both the plasma and liver homogenate.[3] In contrast, the simultaneous administration of T4 and carnitine caused a reduction in the activity of each enzyme. Clinical studies were limited to just a few naturally hyperthyroid or iatrogenically hyperthyroid patients who were treated with 1 to 3 g per day of L-carnitine for a few weeks.[4–7] An improvement in symptomatology was reported, although these clinical studies were unblinded and devoid of statistical analysis. Because improvement in the hyperthyroid symptomatology occurred with no reduction in thyroid hormone levels or reduction of thyroid radioiodine uptake, it was concluded that L-carnitine was acting in the periphery, namely, as an inhibitor of thyroid hormone action in thyroid hormone target tissues, and not at the level of the thyroid gland as an inhibitor of thyroid hormone synthesis.[4–7]

We were surprised that these studies were not pursued further because we still lack an ideal antagonist of thyroid hormone action. Hence, we wished to (a) evaluate the mechanism for the peripheral antagonism of thyroid hormone action[8] and (b) duplicate the beneficial clinical effects with a controlled trial.[9]

BASIC STUDIES

Because thyroid hormone action is mostly mediated by specific nuclear receptors and because occupancy of these receptors is governed by the amount of thyroid hormone present in the cell nuclei, we wished to evaluate whether L-carnitine inhibition of thyroid hormone action in the cells could be due to one or more of the following mechanisms: (i) facilitation of thyroid hormone efflux (exit) from cells; (ii) inhibition of thyroid hormone entry into the cell; (iii) inhibition of thyroid hormone entry into the cell nuclei; and (iv) inhibition of thyroid hormone binding to the nuclear receptors. To address these issues, we used three cell lines as representative of three different cell types that are responsive to thyroid hormones: fibroblasts, hepatocytes, and neurons. Human skin fibroblasts (GM002674 cell line) was from the Human Genetic Repository (Camden, NJ); human hepatocytes were the HepG2 cell lines from the American Type Culture Collection (ATCC, Rockville, MD); and neurons were the mouse neuroblastoma NB41A3 cells (ATCC). All cells were first grown in flasks and then seeded in the recommended growth medium until confluency in plates kept in a humidified CO_2 incubator at 37°C. All data are presented as the mean ± SD (basic studies) or mean ± SE (clinical studies), and either the two-tailed Student's *t* test (basic studies) or ANOVA (clinical studies) was used for statistical differences between means.

In preliminary experiments, confluent cells were incubated with 300 nM ^{14C}L-carnitine for up to 6 h at 37°C in the absence or presence of excess unlabeled L-carnitine to determine the specific (saturable) whole-cell uptake (WCU). Expressed in moles per million cells, WCU was 500 fmoles, 40 pmoles, and 12 nmoles in the NB41A3, fibroblasts, and HepG2 cells, respectively. Half-maximal inhibition of WCU was caused by 20 mM, 10 μM, and 5 mM unlabeled L-carnitine, respectively, consistent with the K_m value for the active transport of carnitine in the corresponding

tissues. In the same preliminary experiments, no ^{14C}L-carnitine activity was detected in the nuclei of all three cell lines during the 6 h of incubation at 37°C.

To evaluate whether the effect of L-carnitine consisted of less hormone being available for thyroid hormone nuclear receptor occupancy through increased thyroid hormone exit from cells, each cell line was allowed to internalize 25 pM ^{125}I-T4 or ^{125}I-T3 for 2 h at 37°C in the incubator. Incubation was in the absence or presence of excess unlabeled L-T4 or L-T3 to determine specific (saturable) WCU. At the end of the 2-h incubation, hormone internalization was stopped by chilling the plates. After three washings of the exterior of the cells with ice-cold phosphate buffer saline (PBS), WCU was determined. After the third washing, cells were incubated with either buffer (control plates) or increasing concentrations of L-carnitine (0.1 nM to 0.1 M) for up to 240 min at 37°C. With the amount of either ^{125}I-T4 or ^{125}I-T3 released into the medium in the presence of buffer at any given time point set at 100, L-carnitine changed that value insignificantly (i.e., by ±5%), regardless of cell line and hormone. From these experiments, we concluded that L-carnitine did not deplete the cell content of either T3 or T4 via an increased efflux of the corresponding hormone.

The other two possibilities were tested in similar sets of experiments. The three cells lines, seeded in plates, were first incubated with 25 pM ^{125}I-T4 or ^{125}I-T3 at 37°C for up to 240 min. Incubation of either radiolabeled hormone occurred in the absence (control) or presence of increasing concentrations of L-carnitine. At different time points of the 240-min time course, hormone uptake was stopped by chilling the plate, and specific WCU was measured in the whole cell and, after subsequent manipulations with hypotonic buffers and centrifugation, in the cell nuclei. Regardless of cells and hormone, saturable WCU was scarcely reduced, while saturable nuclear uptake (NU) was reduced greatly. The highest concentration tested (100 mM) caused a reduced saturable WCU of T3 by 10 ± 1% in NB41A3 cells, 20 ± 2% in HepG2 cells, and 21 ± 2% in fibroblasts, with the last two inhibitions being statistically greater than the 10% inhibition in the neuronal cells ($P < 0.001$). Inhibition of T4 matched inhibition of T3 in a given cell line: 10 ± 1% (NB41A3), 22 ± 2% (HepG2), and 23 ± 2% (fibroblasts). The lowest concentrations of L-carnitine that gave an inhibition of either T3 or T4 WCU statistically different from control ($P < 0.05$) were ~40 mM in NB41A3 cells and 1 mM in the other two cell lines.

At the highest tested concentration of L-carnitine (50 mM), inhibition of saturable NU was 61 ± 4% in NB41A3 and 70 ± 5% in HepG2 cells (not tested in fibroblasts). In NB41A3, inhibition of saturable NU of T4 was also tested and found to be 90 ± 4%. Comparisons of saturable NU of T4 with saturable NU of T3 at the same concentration of L-carnitine over the wide range of L-carnitine concentrations tested (1 to 50 mM) showed that, in the NB41A3 cells, inhibition of saturable NU of T4 was greater than inhibition of saturable NU of T3 ($P < 0.001$). Thus, half-maximal inhibition of T4 saturable NU was observed at ~4 mM L-carnitine, as compared to ~30 mM ($P < 0.001$) for half-maximal inhibition of saturable T3 NU.

From these experiments, we conclude that, assuming the effect of carnitine is on the membrane transporter (carrier) of thyroid hormones, inhibition on the nuclear membrane–associated carrier is much greater than that on the plasma membrane–associated carrier.

That the predominant site of action of carnitine could be the nuclear membrane–associated carrier is suggested by the experiments aimed at testing whether carnitine

affects the binding of thyroid hormones to the nuclear receptors. For this purpose, we incubated ^{125}I-T3 in the absence or presence of increasing concentrations of L-carnitine with nuclei isolated from the three cell lines as described by Ichikawa *et al.*[10] In parallel experiments, nuclei were incubated with ^{125}I-T3 in the absence or presence of increasing concentrations of unlabeled L-T3. While unlabeled L-T3 inhibited binding of ^{125}I-T3 to the nuclei of all three cell lines with the expected K_d of about 1 nM (thus proving that the isolated nuclei indeed contained specific thyroid hormone nuclear receptors), L-carnitine failed to do so.

Taken together, all these experiments indicate that L-carnitine decreases the access of thyroid hormone to thyroid hormone receptors by decreasing the amount of hormone having access to cell nuclei, and not by inhibiting thyroid hormone interaction with the nuclear receptors.

CLINICAL STUDIES (CONTROLLED TRIAL)

Once the experiments described above showed the mechanistic basis for the until then postulated role of L-carnitine as a peripheral antagonist of thyroid hormone action, we conducted a randomized, double-blind, placebo-controlled 6-month trial (FIG. 1) to test the clinical use of L-carnitine.[9] The study was designed to assess both the curative and the prophylactic role, and was performed on 50 adult women not only to avoid gender differences, but also to assess the protection of carnitine against hyperthyroidism-induced osteoporosis. We used the natural model of patients who take thyroid-stimulating hormone (TSH)–suppressive doses of L-T4 to decrease the size of benign thyroid nodules, based on the fact that TSH is a growth factor for

TABLE 1. Symptoms evaluated in the 50 patients in the trial

Symptoms	Evaluation	Direction of change in hyperthyroidism
Asthenia	Subjective 5-point scale (score 1 to 5)	Increase
Dyspnea	Subjective 5-point scale (score 1 to 5)	Increase
Palpitations	Subjective 5-point scale (score 1 to 5)	Increase
Nervousness	Subjective 5-point scale (score 1 to 5)	Increase
Insomnia	Subjective 5-point scale (score 1 to 5)	Increase
Tremors	Subjective 5-point scale (score 1 to 5)	Increase
Knee reflexes	Subjective 5-point scale (score 1 to 5)	Increase
Heart rate	Beats per min, by cardiac auscultation	Increase
Body weight	Kilograms (kg), using the same scale	Decrease

NOTE: At each of the 7 visits (entry and months 1, 2, 3, 4, 5, and 6), patients were required to score their subjective symptoms on this 5-point scale: 1, absent; 2, occasional, but disturbing when present; 3, frequent, disturbing; 4, more frequent, more disturbing; 5, constant, intolerable. Hand tremors were evaluated on this 5-point scale: 1, absent; 2, very fine; 3, fine; 4, mildly gross; 5, overtly gross, shaking of the hands. Knee reflexes were evaluated on this 5-point scale: 1, normal; 2, barely brisk; 3, moderately brisk; 4, markedly brisk; 5, extremely exaggerated, polyphasic.

TABLE 2. Biochemical parameters of thyroid hormone action evaluated in the 50 patients in the trial

Parameters	Target tissue of thyroid hormone action	Change in hyperthyroidism
ALT	Liver	Increase
AST	Liver	Increase
GGT	Liver	Increase
SHBG	Liver	Increase
Ferritin	Liver	Increase
Total cholesterol	Liver	Decrease
CPK	Skeletal muscle	Decrease
Osteocalcin	Bone (osteoblasts)	Increase
Urinary OH-proline	Bone (osteoclasts)	Increase

NOTE: At each of the 7 visits (entry and months 1, 2, 3, 4, 5, and 6), patients were sampled not only for the 9 parameters listed in the table, but also for thyroid parameters (to assess compliance to L-T4 therapy and monitor biochemical hyperthyroidism) and 24-h urinary excretion of carnitine (to assess compliance to L-carnitine ingestion). Patients knew that 24-h urine collection was for measurement of hydroxyproline and ignored the additional purpose of carnitine assay.

ABBREVIATIONS: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyltransferase; SHBG, sex hormone binding globulin; CPK, creatine phosphokinase; OH-proline, hydroxyproline.

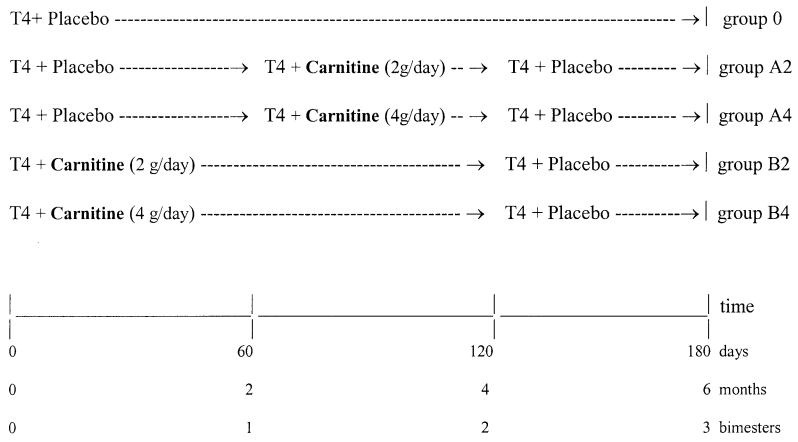

FIGURE 1. Schema of the randomized, double-blind, placebo-controlled trial, with crossover between placebo and L-carnitine in two of the five arms. Each arm (group 0, A2, A4, B2, and B4) consisted of 10 patients each, all women. L-T4 was given in the same normalized dose (2.0–2.4 μg/kg/body weight per day) for the 180 days of the trial and was taken 2–3 h before breakfast to maximize intestinal absorption. Patients took no other medication and had not taken L-carnitine prior to the trial.

nodules. In pilot studies, we had observed that L-carnitine does not antagonize the physiologic negative feedback of thyroid hormones on TSH secretion.

The TSH-suppressive therapy uses doses of L-T4 (≥2.0 μg/kg body weight/day) that are higher than the substitutive ones, thus eliciting one or more hyperthyroid symptoms (TABLE 1); in our trial, L-T4 was administered for the entire 6-month duration. In addition to symptoms, biochemical parameters of thyroid hormone action were evaluated (TABLE 2). For the curative side of the study, we elected to introduce the crossover methodology. In practice, for the curative goal, we challenged the patients in the A groups (FIG. 1) with a TSH-suppressive dose of L-T4 plus placebo for the first 2 months, and induced hyperthyroid symptoms. We switched placebo with carnitine in the subsequent 2 months (to evaluate possible improvement of symptoms) and switched back to placebo in the last 2 months (to evaluate possible relapse of symptoms). For the prophylactic side of the trial, the patients in the B groups (FIG. 1) associated L-T4 with carnitine for the first 4 months (to evaluate possible absence of hyperthyroid symptoms) and then switched carnitine with placebo in the last 2 months (to evaluate possible appearance of symptoms). In each group, bone mineral density (BMD) was evaluated at entry and at end of the trial. To test dose-effectiveness, patients received 2 or 4 g/day carnitine. A control group (group 0, FIG. 1) for both the curative and prophylactic purposes was formed and consisted of patients who associated L-T4 plus placebo for all 6 months.

Data on Compliance to Thyroid Hormone and Carnitine Administration

In all 50 patients, serum TSH was suppressed (<0.01 mU/L) at the first month visit and remained so through the end of the trial. Serum FT3 and FT4 increased at comparable levels in each of the five groups of patients: FT3 at upper normal limits and FT4 at slightly above normal levels (data not shown). Thus, all patients not only were compliant to L-T4 therapy, but they were exposed to the same degree of biochemical hyperthyroidism.

Compared to baseline levels, in patients in groups A and B, the 24-h urinary excretion of carnitine peaked only during the second bimester (A patients) and during both the first and second bimester (B patients); in groups A4 and B4, the increase was double (or ~14 times more than the baseline levels) of that in groups A2 and B2 (~7 times more than the baseline levels). In groups A and B, urinary carnitine dropped, although it was greater than the baseline levels in the third bimester (when patients switched to placebo). Finally, in group 0 patients, there was a slight, progressive increase in the 24-h urinary excretion of carnitine, which at day 180 (end of trial) was approximately threefold greater than baseline values.

Thus, not only were patients compliant to carnitine treatment, but hyperthyroidism per se, as known, stimulates carnitine excretion, thus impoverishing the tissue deposits of carnitine.

Effectiveness of Carnitine—Clinical Parameters

In regard to the curative effect of carnitine, symptoms in groups 0 and A (when all 30 women were taking L-T4 + placebo) changed in the hyperthyroid direction (worsened) with respect to baseline (pretherapy) so that the sign for change was positive for all parameters except body weight (whose change in the hyperthyroid

TABLE 3. Mean ± SE percent changes of the 9 clinical parameters evaluated in the 50 patients in the trial[a]

	Curative effect[b]			Prophylactic effect[c]		
Symptoms	Group 0	Group A2	Group A4	Group 0	Group B2	Group B4
Asthenia	9 ± 3	−29 ± 5	−43 ± 2	50 ± 13	−22 ± 6	−32 ± 4
Dyspnea	10 ± 6	−15 ± 6	−15 ± 4	25 ± 10	−10 ± 5	−11 ± 5
Palpitations	12 ± 6	−35 ± 6	−39 ± 3	52 ± 13	−18 ± 6	−23 ± 6
Nervousness	18 ± 10	−33 ± 8	−31 ± 5	62 ± 11	−26 ± 6	−24 ± 7
Insomnia	18 ± 11	−29 ± 5	−21 ± 5	37 ± 12	−12 ± 5	−23 ± 6
Tremors	18 ± 10	−22 ± 6	−25 ± 5	40 ± 12	7 ± 8	12 ± 8
Knee reflexes	21 ± 5	−20 ± 5	−17 ± 6	37 ± 9	−1 ± 5	6 ± 9
Heart rate	2 ± 3	−7 ± 1	−7 ± 1	10 ± 1	−3 ± 1	−4 ± 1
Body weight	−0.8 ± 0.1	−0.5 ± 0.1	−0.3 ± 0.2	−0.8 ± 0.2	−0.6 ± 0.1	−0.5 ± 0.1

[a]For the curative effect, percent change refers to the second bimester score, beats per min, or kg body weight over the corresponding value of the first bimester × 100. For the prophylactic effect, percent change refers to the pooled first two bimester value over the corresponding baseline (day 0) value. For each group, $n = 10$.

[b]All comparisons between the 3 groups were analyzed by ANOVA and yielded values of $P < 0.001$, except dyspnea, palpitations, insomnia (all $P < 0.01$), and body weight ($P > 0.05$). Concerning difference in carnitine dose (A2 vs. A4), only asthenia improved significantly ($P < 0.05$) at the higher dose.

[c]All comparisons between the 3 groups were analyzed by ANOVA and yielded values of $P < 0.001$, except dyspnea, reflexes ($P < 0.01$), tremors ($P < 0.05$), and body weight ($P > 0.05$). There was no statistical difference ($P > 0.05$) in carnitine dose (B2 vs. B4) for any symptom.

direction, or worsening, is indicated by a decrease and therefore by a negative sign). The changes are not shown, but were of the same magnitude for a given parameter in groups 0, A2, and A4. When group 0 patients continued their intake during the second bimester (months 3 and 4), all 8 positively regulated symptoms continued to worsen with respect to the first bimester. This worsening is indicated by the positive sign of change in TABLE 3.

In contrast, the 8 positively regulated symptoms in women of groups A2 and A4 (who replaced placebo with carnitine during the second bimester) improved as indicated by the negative sign in TABLE 3. The only negatively regulated symptom, body weight, decreased less in groups A2 and A4 as compared to group 0, but the difference was not statistically significant. Overall, the two doses of carnitine were equally effective in reversing the hyperthyroid symptomatology of the first bimester; asthenia, nervousness, and palpitations were the symptoms that benefited the most. Amelioration occurred 1 or 2 weeks after commencement of carnitine.

In regard to the preventive effect, the last three columns of TABLE 3 summarize changes of the symptoms over the first two bimesters (months 1–4) with respect to baseline. All 8 positively regulated parameters responded to iatrogenic hyperthyroidism with a positive change (i.e., worsened) in women of group 0, who started therapy by associating L-T4 with placebo and so continued for the first 4 months of trial. In contrast, the same symptoms in women of groups B2 and B4 (who started

TABLE 4. Mean ± SE percent changes of the 9 biochemical parameters of thyroid hormone action evaluated in the 50 patients in the trial[a]

	Curative effect[b]			Prophylactic effect[c]		
Parameters	Group 0	Group A2	Group A4	Group 0	Group B2	Group B4
ALT	15 ± 5	2 ± 1	3 ± 2	24 ± 3	10 ± 2	8 ± 2
AST	23 ± 2	2 ± 1	−3 ± 2	18 ± 3	−6 ± 3	−9 ± 2
GGT	12 ± 2	−4 ± 7	−7 ± 3	23 ± 2	2 ± 3	−2 ± 3
SHBG	11 ± 2	0 ± 2	−3 ± 1	20 ± 2	10 ± 1	6 ± 1
Ferritin	9 ± 1	−1 ± 2	−4 ± 1	18 ± 2	2 ± 1	−4 ± 1
Total cholesterol	1 ± 1	4 ± 2	4 ± 1	−13 ± 1	−10 ± 1	−7 ± 2
CPK	−10 ± 3	4 ± 1	8 ± 3	−23 ± 2	−10 ± 1	−7 ± 2
Osteocalcin	7 ± 1	18 ± 2	19 ± 2	22 ± 1	32 ± 3	36 ± 4
Urinary OH-P	4 ± 1	5 ± 1	4 ± 1	26 ± 4	27 ± 2	28 ± 2

[a]For the curative effect, percent change refers to the second bimester concentration in serum or urine over the corresponding concentration of the first bimester × 100. For the prophylactic effect, percent change refers to the pooled first two bimester concentration over the corresponding baseline (day 0) concentration. For each group, $n = 10$.

[b]All comparisons between the 3 groups were analyzed by ANOVA and yielded values of $P < 0.001$, except ALT, GGT ($P < 0.05$), cholesterol, and urinary OH-proline ($P > 0.05$). There was no statistical difference ($P > 0.05$) in the carnitine dose (A2 vs. A4) for any parameter.

[c]All comparisons between the 3 groups were analyzed by ANOVA and yielded values of $P < 0.001$, except osteocalcin ($P < 0.01$), cholesterol ($P < 0.05$), and urinary OH-proline ($P > 0.05$). There was no statistical difference ($P > 0.05$) in the carnitine dose (B2 vs. B4) for any parameter, except ferritin ($P < 0.01$) and SHBG ($P < 0.05$).

therapy with L-T4 plus carnitine and so continued for the first 4 months) showed a negative change or, in the case of tremors, a less-positive change. As noted above for the negatively regulated parameter (body weight), the change was more negative in group 0 women, but less negative in groups B2 and B4, although the difference was not statistically significant. Overall, the two doses of carnitine were equally effective in preventing (or minimizing) the hyperthyroid symptomatology of the first 4 months; asthenia, nervousness, and palpitations were the symptoms that benefited the most. Amelioration occurred 1 or 2 weeks after commencement of carnitine.

Effectiveness of Carnitine—Biochemical Parameters

There are no circulating parameters that can be measured as the biochemical equivalent of, for instance, asthenia or tendon reflexes. The biochemical parameters that we measured are those accepted as reflecting the end result of the biological action of thyroid hormones in peripheral tissues via nuclear receptors; the peripheral tissue evaluated predominantly by these biochemical parameters is liver.

The data summarized in TABLE 4 are similar to those presented for symptoms (TABLE 3). In particular, the positively regulated parameters changed in the hyperthyroid direction in group 0 women, whereas they changed in the same direction, but to a much lower extent, or in the opposite direction (i.e., with negative sign) in groups A2, A4, B2, and B4. There were, however, two remarkable exceptions:

TABLE 5. Mean ± SE percent change in BMD at the end of trial with respect to BMD at entry

	Group 0 ($n = 7$)	Group A2 ($n = 6$)	Group A4 ($n = 8$)	Group B2 ($n = 6$)	Group B4 ($n = 8$)
Vertebral BMD	–0.62 ± 0.86	0.44 ± 0.83	1.30 ± 0.88	1.78 ± 0.80	2.26 ± 0.95
Left femur BMD	0.20 ± 0.33	0.37 ± 0.35	0.60 ± 0.39	0.98 ± 0.42	1.34 ± 0.52

NOTE: In each group, patients were fewer than 10 because not all patients reported for the final BMD evaluation. Differences between group 0 vs. A2 and A4 or group 0 vs. B2 and B4, as analyzed by ANOVA, were not statistically significant ($P > 0.05$). In a pairwise comparison, only vertebral BMD of group B4 was statistically different ($P < 0.05$) from vertebral BMD of group 0.

osteocalcin and urinary OH-proline. Osteocalcin, a marker of osteoblastic activity, changed even more in the hyperthyroid direction in groups A2 and A4, as well as in groups B2 and B4, as compared to group 0. Urinary OH-proline, a marker of osteoclastic activity (or bone resorption), changed to the same degree in all five groups. However, these are beneficial changes (i.e., more bone is formed), not detrimental ones. Concerning the two negatively regulated parameters, CPK was sensitive to carnitine inhibition of thyroid hormone action (i.e., less-negative change in groups B2 and B4, and positive change in groups A2 and A4, as compared to group 0).

Effectiveness of Carnitine—Bone Mineral Density

Clinically relevant to support the beneficial effect on bone shown by the aforementioned changes in osteocalcin and urinary OH-proline are the data on BMD (TABLE 5). Although not statistically significant because of few patients and the short term of therapy employed, it is noteworthy that the groups with the greatest values of either vertebral or femur BMD were, consistently, the groups that received carnitine. A trend towards a dose-effect of carnitine is evident because BMD is greater in A4 vs. A2 and B4 vs. B2.

CLINICAL STUDIES (THYROID STORM)

One might argue that iatrogenic hyperthyroidism is a relatively mild state of thyroid hormone excess in blood. This is not entirely correct because a number of patients respond greatly to small increases of circulating thyroid hormones, and they typically reduce the dose of L-T4 or even stop therapy. After conclusion of our trial,[9] two of us (S.B. and F.T., unpublished data) have used L-carnitine (Carnitene™, Sigma-Tau, Rome, Italy) in other forms of hyperthyroidism, such as that associated with postpartum thyroiditis (PPT), subacute thyroiditis (SAT), Hashitoxicosis (HT), amiodarone therapy of supraventricular arrhythmias, autonomous nodular goiter (ANG), and Graves' disease. Basically, L-carnitine was given to control the transient course and moderate level of hyperthyroidism associated with PPT, SAT, and HT. For the other conditions, reasons for use of carnitine (alone or in combination with low doses of conventional antithyroid drugs [methimazole, propylthiouracil]) were the moderate level of hyperthyroidism and/or side effects by the antithyroid drugs,

or, in the case of amiodarone-induced hyperthyroidism, side effects by perchlorate. The old clinical studies mentioned in the INTRODUCTION[4–7] were conducted on patients with Graves' disease using 1–3 g/day carnitine.

Two of us[11] had the opportunity to use L-carnitine in a serious form of hyperthyroidism: thyroid storm (or thyroid crisis). Thyroid storm is typically triggered by precipitating events, is lethal in over half of the cases, and requires high doses of antithyroid drugs. The patient we described was a young male who had his first episode (onset) of Graves' disease 2 years earlier. The thyroid storm we observed 2 years later could be treated with 10–15 mg/day methimazole (as opposed to doses of ~100 mg/day that are typical for thyroid storms) because of leukopenia and thrombocytopenia, plus 2 g/day Carnitene™ (enteric vials). Over the following 5 months, two additional relapses (favored by the low doses of antithyroid drug used) of thyroid crisis occurred. However, although the magnitude of biochemical hyperthyroidism (elevation of serum FT3 and FT4) was comparable to that of the first storm, hyperthyroid symptomatology was milder. Incidentally, the fact that carnitine failed to prevent relapses of hyperthyroidism further supports the concept that carnitine action is in the periphery and not in the thyroid gland.

Since hyperthyroidism is a cause of acquired carnitine deficiency, there is a rationale for using L-carnitine at least in certain clinical settings.

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