Usefulness of L-Carnitine, A Naturally Occurring Peripheral Antagonist of Thyroid Hormone Action, in Iatrogenic Hyperthyroidism: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Old studies in animals and unblinded studies in a few hyperthyroid patients suggested that L-carnitine is a periferal antagonist of thyroid hormone action at least in some tissues. This conclusion was substantiated by our recent observation that carnitine inhibits thyroid hormone entry into the nucleus of hepatocytes, neurons, and fibroblasts. In the randomized, double-blind, placebo-controlled 6-month trial reported here, we assessed whether 2 or 4 g/d oral L-carnitine were able to both reverse and prevent/minimize nine hyperthyroidism-related symptoms. We also evaluated changes on nine thyroid hormone-sensitive biochemical parameters and on vertebral and hip mineral density (bone mineral density). Fifty women under a fixed TSH-suppressive dose of L-T_4 for all 6 months were randomly allocated to five groups of 10 subjects each. Group 0 associated placebo for 6 months; groups A2 and A4 started associating placebo (first bimester), substituted placebo with 2 or 4 g/d carnitine (second bimester), and then returned to the association with placebo. Groups B2 and B4 started associating 2 and 4 g/d carnitine for the first two bimesters, and then substituted carnitine with placebo (third bimester).

Symptoms and biochemical parameters worsened in group 0. In group A, symptoms and biochemical parameters worsened during the first bimester, returned to baseline or increased minimally during the second bimester (except osteocalcin and urinary OH-proline), and worsened again in the third bimester. In group B, symptoms and biochemical parameters (except osteocalcin and urinary OH-proline) did not worsen or even improved over the first 4 months; they tended to worsen in the third bimester. In both the A and B groups, the two doses of carnitine were similarly effective. At the end of the trial, bone mineral density tended to increase in groups B and A (B > A).

In conclusion, L-carnitine is effective in both reversing and preventing symptoms of hyperthyroidism and has a benefical effect on bone mineralization. Because hyperthyroidism depletes the body deposits of carnitine and since carnitine has no toxicity, teratogenicity, contraindications and interactions with drugs, carnitine can be of clinical use. (*J Clin Endocrinol Metab* 86: 3579–3594, 2001)

L-CARNITINE IS A quaternary amine (β-hydroxy-γ-trimethylammonium butyrate) that is ubiquitous in biological fluids and tissues of mammals, where it plays an important role in energy metabolism (1–4). Primary and secondary deficiencies of carnitine, including the depletion of cardiac carnitine associated to coronary heart disease and heart failure, are the therapeutic indications for carnitine (1). Oral doses usually range between 1 and 4 g per day (1).

Old studies in animals showed that carnitine is capable of contrasting thyroid hormone-driven changes associated with the metamorphosis of tadpoles and the nitrogen balance of rats (5–7). The same group of authors (7) also showed that serum and liver concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were increased in rats treated with T_4, but were decreased in rats treated with carnitine. These studies were followed by unblinded studies on a small number of thyrotoxic patients, who were treated solely with 1–3 g per day oral carnitine for a few weeks

(8–11). Although quantification of the symptomatology and statistical analysis were lacking, the authors (8–11) reported a definitive improvement in the symptomatology starting from the second week of treatment; goiter size, thyroid [^{131}]I uptake, ophthalmopathy, and serum protein-bound iodine were unchanged (8–11). Carnitine was, thus, considered to be a peripheral antagonist of thyroid hormone action, not an inhibitor of the thyroid gland function (8–11).

Considering that until now we lack an ideal antagonist of thyroid hormone action, it is quite surprising that no subsequent studies were performed. We have developed an interest for carnitine and have found that it inhibits thyroid hormone entry into the nucleus of human and animal cells (fibroblasts, hepatocytes, neurons) (12), thus explaining the peripheral antagonism. Based on this experimental evidence (12), we wished to conduct a controlled trial to test the clinical use of carnitine.

Patients and Methods

Generalities

We tested the possible benefits of carnitine in adult women (namely, the vast majority of thyroid patients) under TSH-suppressive doses of

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L-thyroxine for benign nodular goiter. We preferred these patients to Graves' disease patients for several reasons, among which the additional drugs and/or nonmedical modalities of therapy that the latter patients might require, thus complicating the study. Moreover, with our protocol we could evaluate a double effect of carnitine, namely whether it was capable of both reversing and preventing hyperthyroidism.

In pilot studies on humans, we observed that carnitine does not antagonize the physiological negative feedback of thyroid hormones on TSH secretion.

Study design (protocol)

This randomized, double-blind, placebo-controlled trial with cross-over between placebo and carnitine had been approved by the Ethical Committee of our University. Criteria for entry, after signature of the informed consent form, were: 1) to be in good health, based on thorough physical examination and routine clinical chemistry; 2) no previous use of thyroid hormones and carnitine; and 3) no use of other medications.

Patients were randomly allocated to three major groups of 10 persons each: 0 (zero, meaning no carnitine at any time), A and B. All patients, who were euthyroid at baseline, received 2.0–2.4 μg per kg body weight per day (13) oral L-thyroxine (Eutirox; Bracco, Milan, Italy), which was taken 2–3 h before breakfast to maximize intestinal absorption (14). Although not necessary in a cross-over study, group 0 served as a surrogate group, namely it served to show what could have happened to group A and B patients if treated with L-thyroxine alone. Groups A and B consisted of two subgroups each (A2, A4, B2, B4), based on the daily oral dose (2 or 4 g, when indicated) of L-carnitine; clearly, the two subgroups served to evaluate possible dose-dependency of the carnitine effects. L-carnitine (Carnitene, enteral liquid vials of 1 or 2 g; Sigma-Tau, Pomezia, Italy) was taken twice daily (1 vial after lunch, 1 vial after dinner). In group A, L-thyroxine was associated with placebo from d 1 through 60 or with carnitine during d 61 through 120 or again with placebo during d 121 through 180. In group B, L-thyroxine was associated to carnitine during d 1 through 120 or placebo during d 121–180. We decided to administer carnitine for 4 months in group B to have a consistent evidence of its effectiveness (4 months, not 2 months).

At day 0, 30, 60, 90, 120, 150, and 180 ($\pm$ 1 day) all 50 patients were evaluated clinically and biochemically (see below). In addition to tablet counting, compliance to L-thyroxine was assessed by measuring serum free thyroid hormones (FT_3, FT_4) and TSH (which had to be ≤ 0.01 mU/l) at all visits. The three hormones were measured with the electrochemi-luminescent assay by Boerhinger (Mannheim, Germany). The corresponding coefficients of variation (CV) are 2.8%, 2.5%, and 2.2% (intra-assay) and 3.9%, 3.8%, and 3.3% (interassay). In addition to vial counting, compliance to carnitine was assessed by measuring the 24-h urinary excretion of carnitine (3) (courtesy of Drs. A. Toscano and M. d'Agennouz, Clinica Neurologica 2, University of Messina), with patients being not aware of this particular scope of the urine collection. Figure 1 shows the compliance to the two drugs and, at the same time, the homogeneity of the five groups in terms of serum hormones.

The mean age ($\pm$SE) in each group was not statistically different from the age of the other groups: 40.0 ± 2.8 (group 0), 48.3 ± 4.2 (A2), 43.4 ± 5.8 (A4), 42.2 ± 2.8 (B2), and 40.1 ± 4.9 yr (B4).

Evaluation of the symptomatology

Other authors (*cf.* 15) have discussed the unnecessary complications of certain "clinical indices" in favor of simple clinical rules. Clinical indices are numerous (*e.g.* Refs. 16–19), as none is satisfactory. The prototype of such indices is the Crooks' index (20), which is a single number resulting from a scoring system based on the presence or ab-
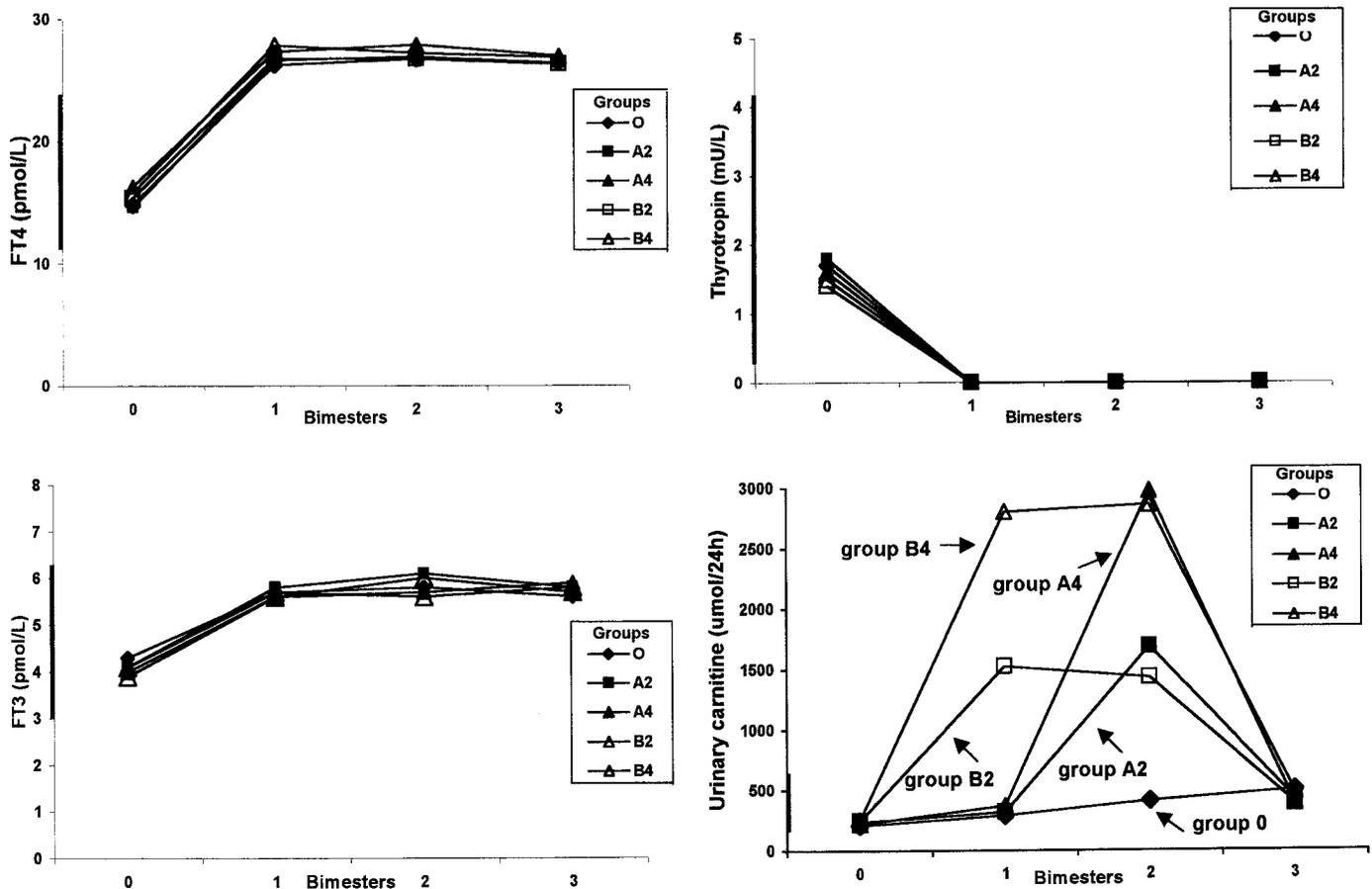

FIG. 1. Changes in serum FT_3, FT_4, TSH, and 24-h urinary excretion of carnitine at entry and during the three bimesters of the clinical trial in the five study groups. Not to complicate the figure, SE bars are not given. Note the overlap in the hormone profiles among groups, and the greater carnitine excretion in the 4 g/d-treated groups (A4, B4) *vs.* the 2 g/d-treated groups (A2, B2).

sence of some symptoms and signs. Present symptoms are assigned different scores (*e.g.* dyspnea +1, palpitations +2, weight decrease +3), which are fixed, so that changes in their severity cannot be quantified.

Based on our experience on hundreds of naturally hyperthyroid patients under antithyroid drug therapy and thousands of patients under TSH suppressive-therapy, we have constructed the 5-point scale presented in Table 1 to quantify symptoms. Compared with the Crooks' index (20), we have omitted sweating, because enrollment and follow-up of different patients occurred in different seasons, and have added insomnia and knee reflexes. On 100 overtly hyperthyroid adult women whose FT_4 had been measured with the same assay used in the present study, the correlation of our scoring system with serum FT_4 was 0.41 ($P < 0.001$, dyspnea) to 0.78 ($P < 0.001$, palpitations) (unpublished data), which are r values better than the 0.36 (P level not given) of the Crooks' index (20) and comparable with the 0.57–0.70 values (P level not given) of the Geffner's index (17). In these 100 patients, the score for each subjective symptom decreased, on the average, by 3-fold or more ($P < 0.02$ to $P < 0.001$ by two-tailed paired Student's t test) once euthyroidism has been restored by antithyroid drug therapy (unpublished data). The magnitude of changes is similar to the variation in 10 symptoms (scored on a 5-point scale from 0 to 4) reported by Klein *et al.* (16) for their 10 medically treated hyperthyroid patients. Symptoms worsened again in the 36 of 100 patients whose hyperthyroidism relapsed.

Patients were required to keep track of changes in frequency, intensity, and tolerability of symptoms. At each monthly visit, patients were interviewed and examined clinically. Clinical examination was performed by any two authors of this study, but separately. A third author served to solve disagreements, but this intervention was necessary at only 4 of the 350 times (50 patients × 7 visits), and it occurred at control visits that were not particularly relevant (fifth or sixth month).

Biochemical evaluation

Although oral doses up to 15 mg L-carnitine per day are well tolerated (1), nevertheless we monitored routine blood chemistry and urine analysis monthly. Among the blood parameters, some are regulated by thyroid hormones. ALT, AST, γ-glutamiltransferase (GGT), and alkaline phosphatase are up-regulated, whereas creatine phosphokinase and cholesterol are down-regulated (21). All these parameters were measured with the IL 900 Autoanalyzer (Instrumental Laboratory, Milan, Italy) using colorimetric kits having intra-assay CV less than 4% and interassay CV less than 6%. For the purpose of this study, sera were stored at -20 C until the trial was completed. Then, each parameter in the 350 samples (7 samples/patient × 10 patients/group × 5 groups) was measured in the same run.

Also, after the end of the trial and in a single run, four additional parameters, all up-regulated by thyroid hormones, were measured: sex hormone-binding globulin (SHBG), ferritin, osteocalcin, and the 24-h urinary excretion of hydroxyproline (OH-P) (21). Serum SHBG and osteocalcin were measured with the imunoradiometric assay by Radim (Pomezia, Italy) and CIS (Gif-sur-Yvette, France), respectively; ferritin with the chemiluminescent assay by Diagnostic Products (Los Angeles, CA); and OH-P with the high-performance liquid chromatography kit

by Bio-Rad Laboratories, Inc. (Hercules, CA). The corresponding intra-assay CV were 5.1%, 3.8%, 5.2%, and 5.2%, whereas the interassay CV were 5.2%, 4.7%, 8.2%, and 6.6%.

Bone density evaluation

Thyroid hormones have a dual effect on bone: stimulation of osteoblasts, with the subsequent increase of markers of bone formation such as serum osteocalcin, and stimulation of osteoclasts, with the subsequent increase of markers of bone resorption such as urinary OH-P (21). Because of this and because of the controversy surrounding the relationship between thyroid hormone treatment on bone (22), we thought it was of interest to complement the biochemical measurements of serum osteocalcin and urinary OH-P with a clinically relevant parameter: bone mineral density (BMD). BMD (g/cm^2) of the lumbar spine (L_2–L_4) and left femur was measured at baseline and end of the trial by dual-energy x-ray absorptiometry using a Hologic QDR-2000 instrument (Waltham, MA). The second or posttreatment BMD could not be always scheduled at the 180th day (± 1 day) (*viz.* the same day of the last visit and blood and urine collection). For this reason, two to four patients in each group did not report themselves to the second BMD. Consequently, the two BMD measurements are available for six to eight subjects per group.

Adverse events

Undesirable clinical symptoms reported by patients were recorded at each visit starting from d 1, based on direct clinical questioning. In addition to vital sign assessment, physical examinations and blood and urine chemistry were conducted at all visits.

Statistical analysis

Data are presented as mean $\pm$ SE; the 95% confidence interval (CI) for changes is also given. Differences between means were analyzed by ANOVA.

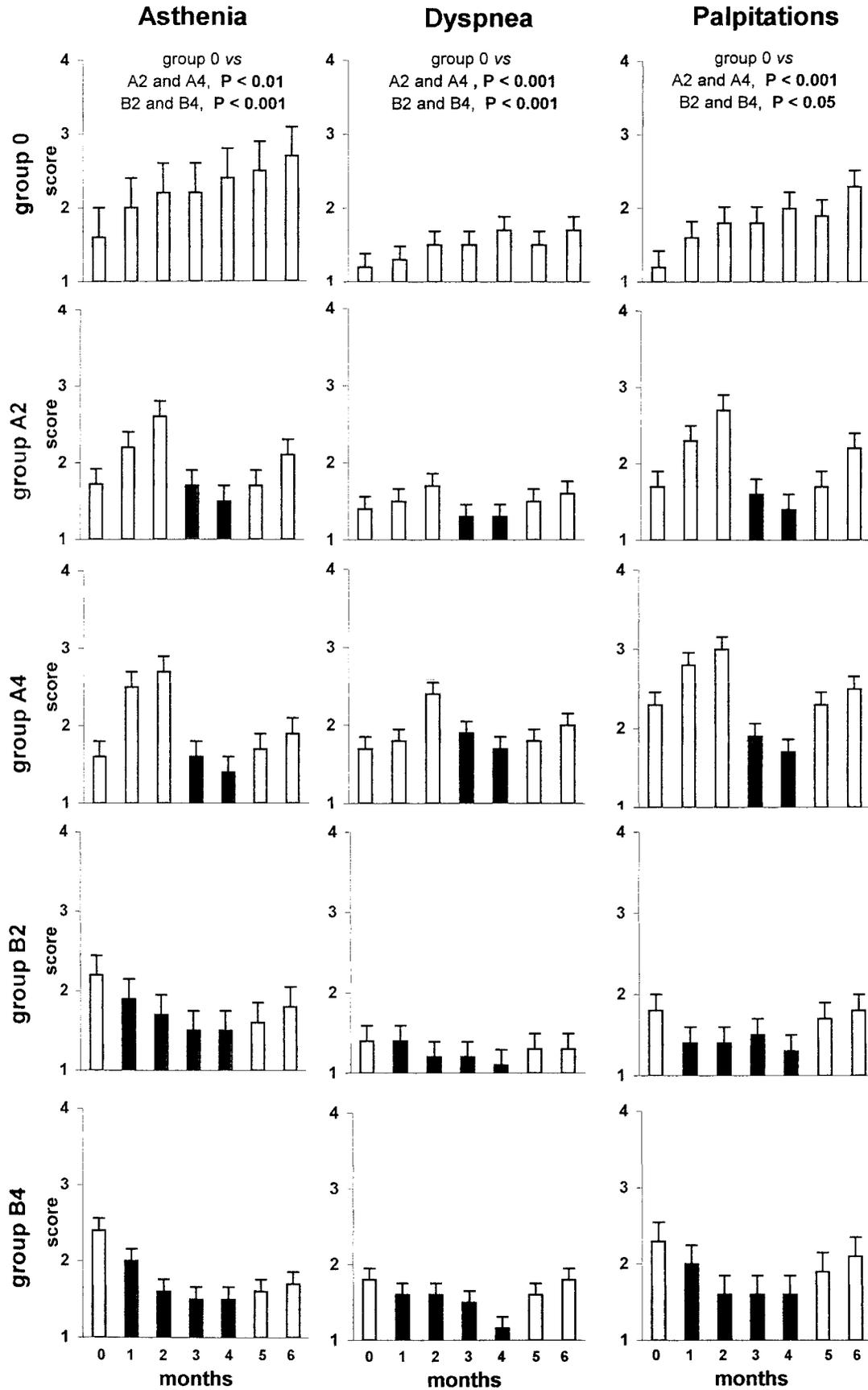The level of statistical significance was set at P less than 0.05.

Results

Changes in serum FT_3, FT_4, TSH, and 24-h urinary excretion of carnitine at entry and during the trial are reported in Fig. 1. As expected, all 50 patients were confirmed to be euthyroid at baseline by thyroid function testing. Differences between groups concerning FT_3, FT_4, and TSH being not statistically significant ($P > 0.05$). Serum FT_3, FT_4, and TSH at entry ranged 4.1 ± 0.2 (group B2) to 4.5 ± 0.2 pmol/l (group 0), 14.8 ± 0.7 (group A2) to 16.5 ± 0.1 pmol/l (group A4), and 1.4 ± 0.4 (group B2) to 1.9 ± 0.5 mU/l (group A2), respectively. At the 1-month visit and thereafter, in all five groups serum FT_3 was in the upper-normal range, serum FT_4

TABLE 1. Standardized evaluation of the symptomatology

Score	Symptomatology		
	Subjective[a]	Objective[b]	
		Tremors	Reflexes
1	Absent	Absent	Normal
2	Occasional but disturbing when present	Very fine	Barely brisk
3	Frequent; disturbing	Fine	Moderately brisk
4	More frequent; more disturbing	Mildly gross	Markedly brisk
5	Constant, intolerable	Overtly gross; shaking of the hands	Extremely exaggerated, polyphasic

[a] Asthenia, dyspnea, insomnia, nervousness, palpitations.
[b] Scoring for tremors virtually coincides with the 5-point scale from 0 to 4 of Klein *et al.* (16): 0, absent; 1, barely perceptible; 2, demonstrated readily on examination; 3, marked; 4, hands shake excessively. We evaluated knee reflexes on the patient seated with legs hanging loosely from the edge of the examining table. With the examiner standing at given distance from resting legs, we defined normal (score 1) legs moving forward by 5–10 cm after percussion of the patellar tendon, and the three-degrees of briskness as legs moving forward by 11–20 cm (score 2), 21–30 cm (score 3), and 31–40 cm (score 4). The other two objective parameters [heart rate (in beats per min) and body weight (in kg)] were evaluated by heart auscultation and by weighing. All patients were weighed with the same scale.

Asthenia

group 0 *vs*
A2 and A4, P < 0.01
B2 and B4, P < 0.001

Dyspnea

group 0 *vs*
A2 and A4 , P < 0.001
B2 and B4, P < 0.001

Palpitations

group 0 *vs*
A2 and A4, P < 0.001
B2 and B4, P < 0.05

was above the upper normal limit, and serum TSH was consistently suppressed (Fig. 1). Again, there were no inter-group statistical differences in the three hormone levels ($P > 0.05$) throughout the trial. Urinary excretion of carnitine at entry ranged from 206 ± 37 (group 0) to 251 ± 4.1 μmol/24 h (group B4) ($P > 0.05$). Urinary carnitine peaked at the time expected (*viz.* months 3 and 4 in both groups A2 and A4; months 1 through 4 in both groups B2 and B4), and with the gradient expected (A4 > A2, and B4 > B2) (Fig. 1), proving that patients were compliant to carnitine administration.

Reversal effect of carnitine

Symptomatology. Modifications of the clinical parameters in groups 0, A2, and A4 are shown in the *top three panels* of Figs. 2-4. The first eight parameters are positively regulated by thyroid hormones; thus, increase indicates worsening. Body weight is negatively regulated; thus, worsening is indicated by a decrease in kilograms. Over the first 2 months of the trial symptoms/signs worsened to a similar extent in the three groups. However, the profile of changes diverged during the following 2 months in group 0 (symptoms increased) *vs.* groups A (symptoms decreased). When placebo was reintroduced in place of carnitine (fifth and sixth month of therapy), symptoms worsened (or tended to) in groups A2 and A4. Overall, during the 6 months of the trial, the intensity of each symptom/sign in the A2 and A4 groups was statistically different from group 0 ($P < 0.05$ to $P < 0.001$) (Figs. 2–4); differences concerning body weight were not significant ($P > 0.05$).

In Fig. 5, the important variations are presented as percentage changes on the same scale for all nine clinical parameters. In these figures, changes brought about by carnitine during the third and fourth month with respect to the first and second month (*i.e.* the first placebo period) in patients of groups A2 and A4 are contrasted with the equivalent changes in patients of group 0 (who continued to take placebo, instead of switching to carnitine). Differences between the two carnitine groups and the placebo group were statistically significant ($P < 0.01$ to $P < 0.001$), but differences between the two carnitine groups were not ($P > 0.05$), except for asthenia ($P < 0.05$). The parameters that changed most were palpitations [35% (CI −48.6 to −21.4%)] and nervousness [33% (CI −49.9 to −15.5%)] in group A2, and asthenia [43% (CI −48.3 to −37.3%)], palpitations [39% (CI −44.7 to −32.8%)] and nervousness [31% (CI −41.5 to −20.1%)] in group A4.

In either A group, clinical amelioration commenced 1 or 2 wk after carnitine administration had been started.

Biochemical parameters. With the exception of TSH (which was illustrated in Fig. 1), creatine phosphokinase and cholesterol, the other biochemical parameters are up-regulated by thyroid hormones. The peripheral parameters in groups 0, A2, and A4 are illustrated in the *top three panels* of Figs. 6-8. Taking into account all data from 0–6 months for any given parameter, groups A2 and A4 were statistically different from group 0 ($P < 0.05$ to $P < 0.001$) (Figs. 6–8). Over the first 2 months, the positively regulated parameters increased in the three groups. However, similarly to the clinical parameters (see above), the profile diverged during the subsequent 2 months in group 0 *vs.* groups A2 and A4, except for cholesterol, osteocalcin, and urinary OH-P.

All these changes, normalized on a percentage basis, can be appreciated in Fig. 9, and they were statistically significant ($P < 0.05$ to $P < 0.001$) but with two exceptions. In fact, variations of cholesterol overlapped ($P > 0.05$) in groups 0 [1.0% (CI −1.7 to 3.7)], A2 [4.0% (CI 0.4–7.5)] and A4 [3.7% (CI 0.43–6.9)], as did variations in OH-P, a marker of bone resorption [3.9% (CI 2.2–5.5), 5.1% (CI 1.8–8.3), and 4.4% (CI 2.2–6.5%), respectively] (Fig. 9). In contrast, the positively regulated osteocalcin, which is a marker of bone formation, increased to a greater extent ($P < 0.001$) in groups A2 and A4 [17.6% and 19.5% (CI 13.9–21.3 and 15.1–23.9)] compared with group 0 [7.0% (CI 4.4–9.6)]. For all parameters, differences between the two doses of carnitine were not statistically significant ($P > 0.05$).

In brief, L-carnitine has 1) an antagonist action on the thyroid hormone-elicited increase of serum AST, ALT, GGT, SHBG, and ferritin; 2) a neutral effect on the thyroid hormone-driven decrease of serum TSH and total cholesterol, and increase of urinary excretion of OH-P; and 3) a potentiating effect on the thyroid hormone-driven increase in serum osteocalcin.

Bone density. Because of the small number of subjects, the increase of posttherapy BMD of either lumbar spine or left proximal femur in groups A was not statistically significant ($P > 0.05$) from the corresponding posttherapy changes observed in group 0 *vs.* groups A (Fig. 10).

Preventive effect of carnitine

Symptomatology. Modifications of the clinical parameters throughout the clinical trial in groups B2 and B4 are illustrated in the *bottom two panels* of Figs. 2–4, and they can be contrasted with the corresponding modifications in group 0 (*top panel* of Figs. 2–4). Except for body weight, the 6-month profile of each parameter (*i.e.* overall increase) in the placebo

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FIG. 2. Variations (mean ± SE) of the three indicated clinical parameters in the five groups of patients throughout the 6-month duration of the trial. Variations of the remaining six clinical parameters are illustrated in Figs. 3 and 4. All patients took TSH-suppressive doses of L-thyroxine from d 1 through 180, which was always associated to placebo in the 10 patients of group 0. In group A2 (n = 10) and A4 (n = 10) patients, who were enrolled to evaluate whether 2–4 g/d oral L-carnitine were able to reverse iatrogenic hyperthyroidism, placebo was associated during months 1, 2, 5, and 6, and carnitine during months 3 and 4 (■). In group B2 (n = 10) and B4 (n = 10) patients, who were enrolled to evaluate whether 2–4 g/d oral L-carnitine were able to prevent iatrogenic hyperthyroidism, placebo was associated during months 5 and 6, and carnitine during months 1 through 4 (■). For each symptom, all data points from 0–6 months in group 0 are compared with all data points in groups A2 and A4 or B2 and B4 by ANOVA, and the resulting *P* value is shown. The relevant percentage changes in severity of each symptom are summarized and contrasted between groups in Figs. 5 and 11. For details on the evaluation of symptomatology, see Table 1 and text (*Patients and Methods*).
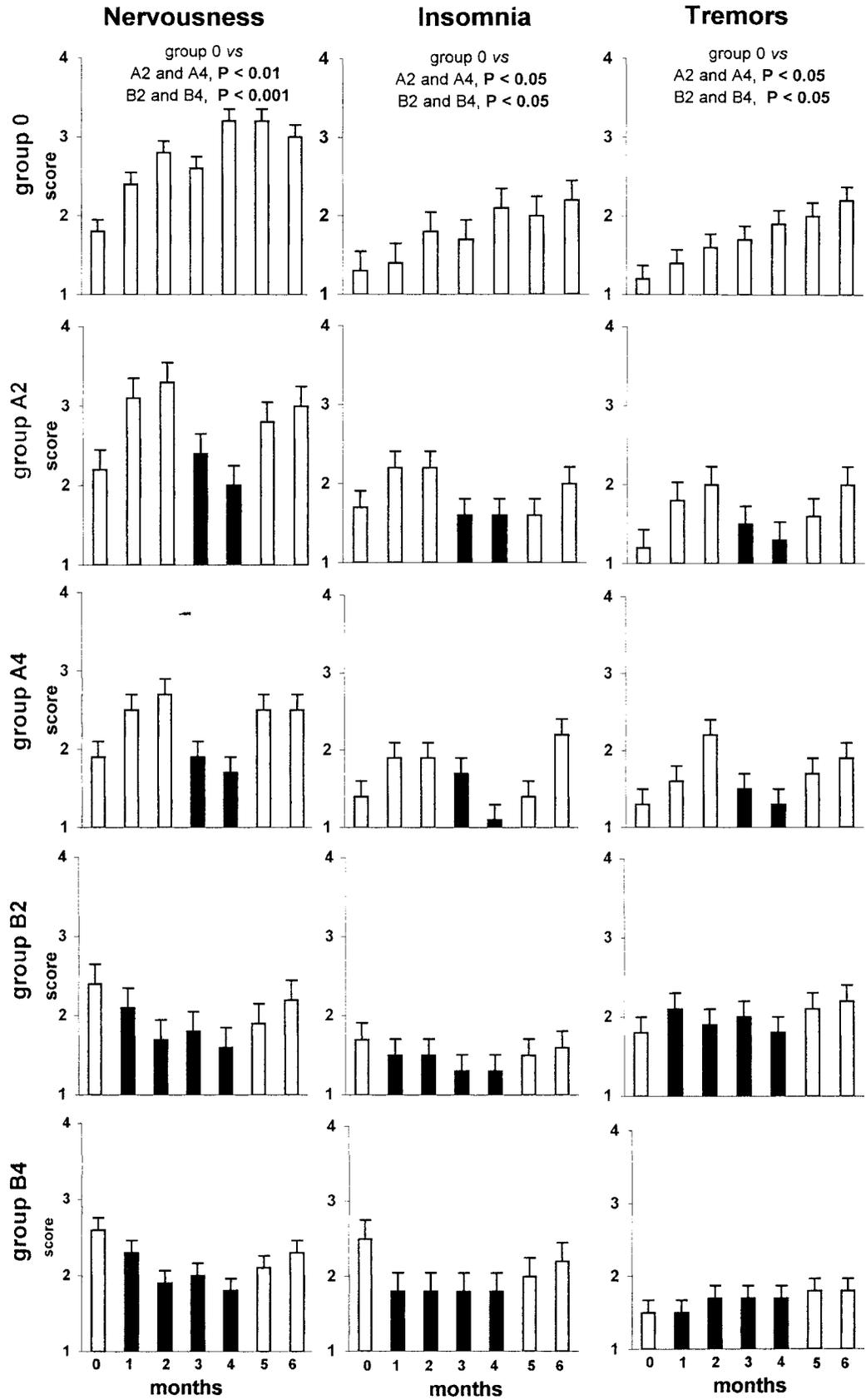
FIG. 3. Variations (mean $\pm$ SE) of the three indicated parameters in the five groups of patients throughout the 6-month duration of the trial. Variations of the remaining six clinical parameters are illustrated in Figs. 2 and 4. For other details, see legend to Fig. 2.
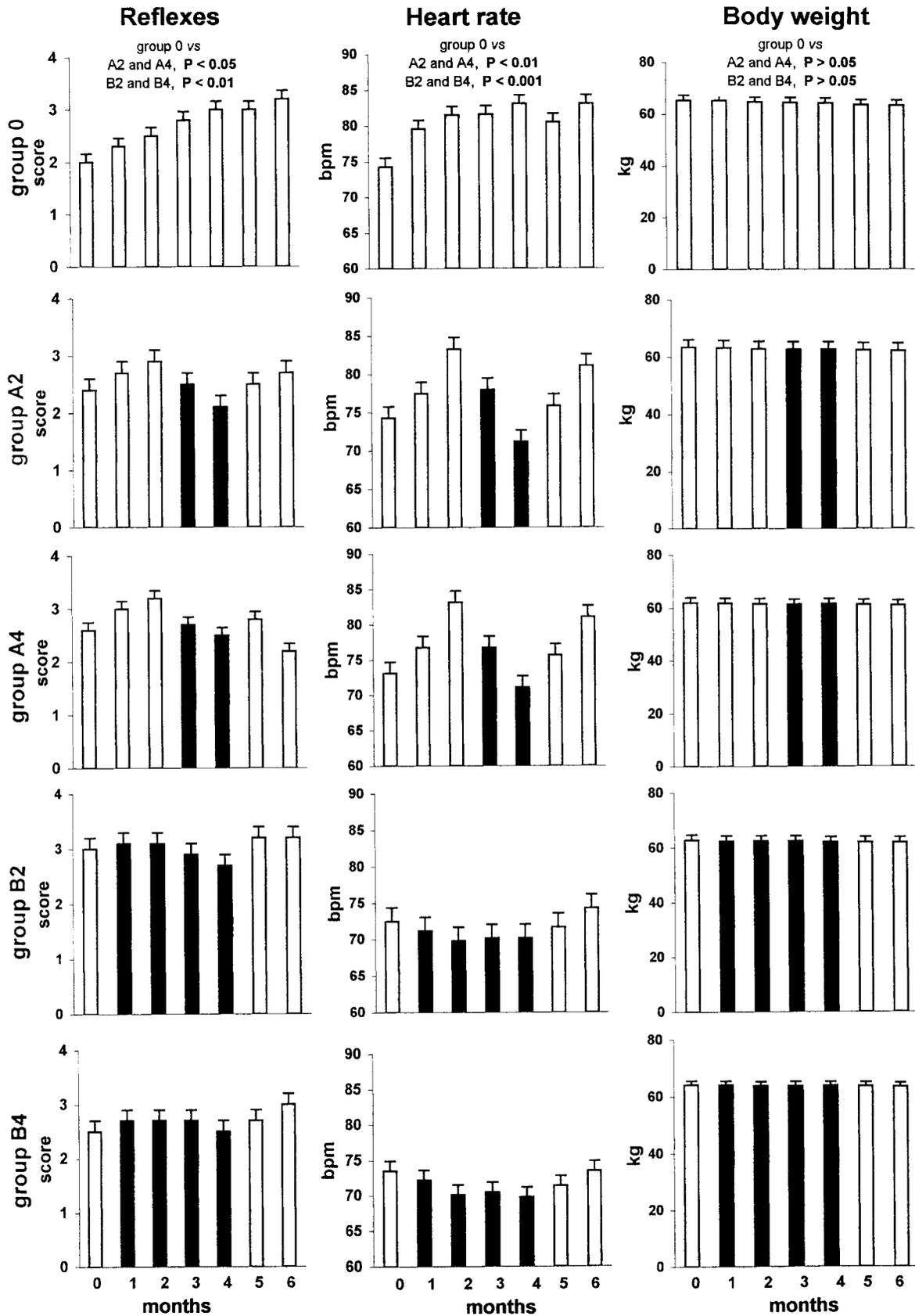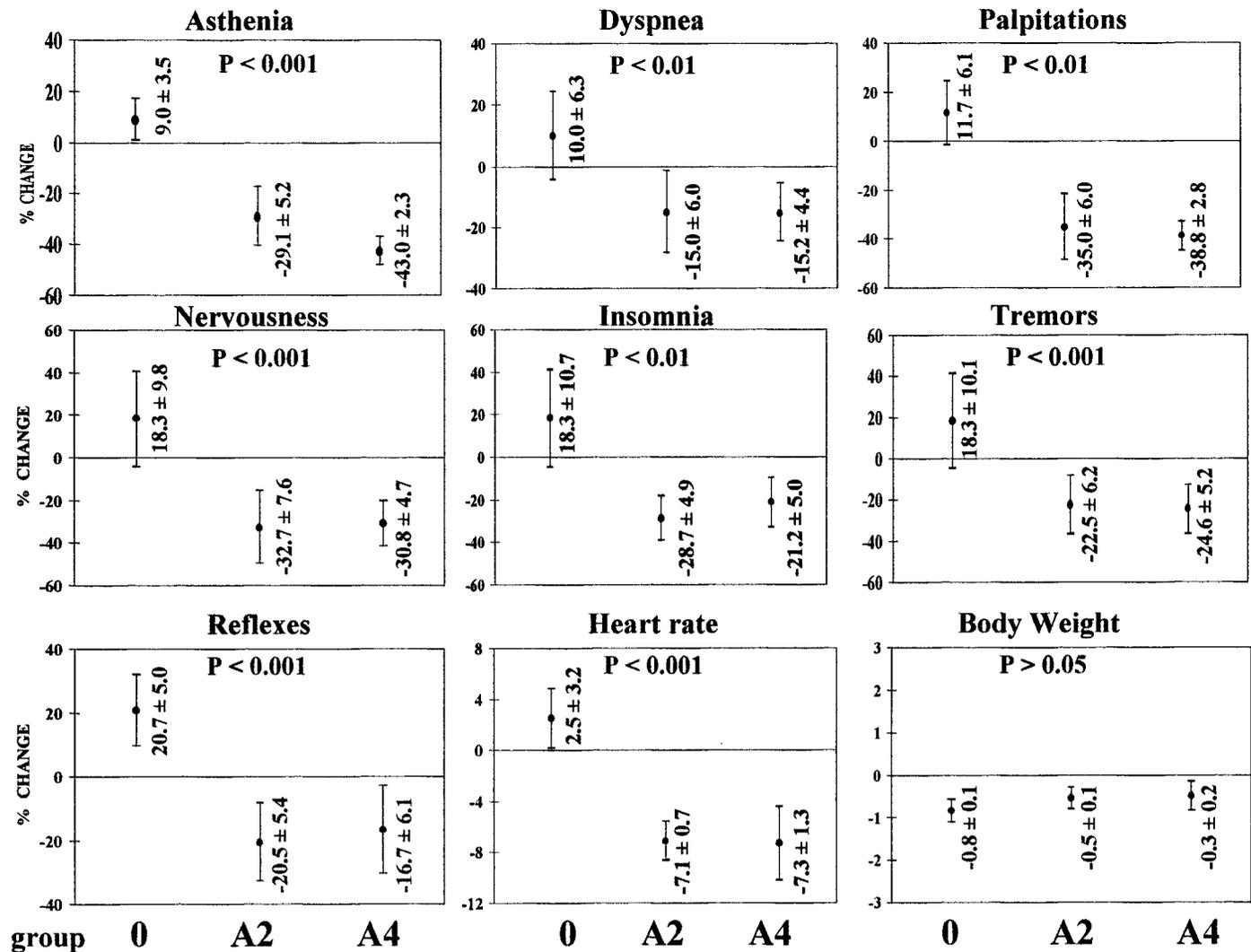
FIG. 4. Variations (mean ± SE) of the three indicated parameters in the five groups of patients throughout the 6-month duration of the trial. Variations of the remaining six clinical parameters are illustrated in Figs. 2 and 3. For other details, see legend to Fig. 2.

FIG. 5. Mean ± SE percentage change and 95% CI of the nine clinical parameters evaluated in group 0, A2, and A4 patients. Percentage change means second bimester score or beats per minute or kg body weight over the corresponding first bimester parameter times 100. During the second bimester, group 0 patients continued to take placebo plus T₄, and their symptoms or signs continued to worsen. In contrast, A2 and A4 patients substituted placebo with carnitine, and their symptoms or signs ameliorated. Only changes in body weight did not differ statistically (*P* > 0.05) in group 0 *vs.* groups A2 or A4.

group was statistically different (*P* < 0.05 to *P* < 0.001) from the two carnitine groups. In these two groups, symptomatology overtly decreased as long as carnitine was maintained, and there was a tendency to worsening during months 5 and 6, when carnitine was replaced by placebo (Figs. 2–4).

In Fig. 11 percentage changes over baseline of the severity of symptoms/signs during the 4 months of adjunctive carnitine treatment in groups B2 and B4 are contrasted with the corresponding changes in group 0 patients, in whom the adjunctive treatment was placebo. Differences between the B2 and B4 groups *vs.* the 0 group were significant (*P* < 0.05 to *P* < 0.001). The largest changes concerned nervousness [26% (−39.6 to −12.8%)] and asthenia [22% (−36.2 to −8.4%)] in group B2, and asthenia [32% (−40.5 to −23.6%)], nervousness [24% (− 40.6 to −6.9%)], palpitations [23% (−37.0 to −8.4%)] and insomnia [−23% (−37.0 to −9.2%)] in group B4. Heart rate decreased by 2.9% (CI −5.2 to −0.6%) or 3.6% (CI

−6.1 to −1.2%) in group B2 or B4, respectively. Similarly to the A groups, the two doses of carnitine were equally effective (Fig. 11), and amelioration lagged 1 or 2 wk behind commencement of carnitine.

Biochemical parameters. Data for the whole duration of the trial are illustrated in the *top panel* (group 0) and the *two bottom panels* (groups B2 and B4) of Figs. 6–8, whereas the relevant percent changes are summarized in Fig. 12. Except for TSH (see Fig. 1) and urinary OH-P, absolute values of the other parameters throughout the 6 months of the trial (Figs. 6–8) and percentage changes during the first 4 months with respect to baseline (Fig. 12) were in group 0 statistically different from groups B2 and B4 (*P* < 0.05 to *P* < 0.001). Confirming the observation in groups A2 and A4 *vs.* group 0, serum osteocalcin increased over baseline to a greater extent (*P* < 0.001) in groups B2 and B4 *vs.* group 0, namely by 32% (CI 25–38.2) and 36% (CI 27–44.6) *vs.* 22% (CI 19.3–24.9) (Fig.
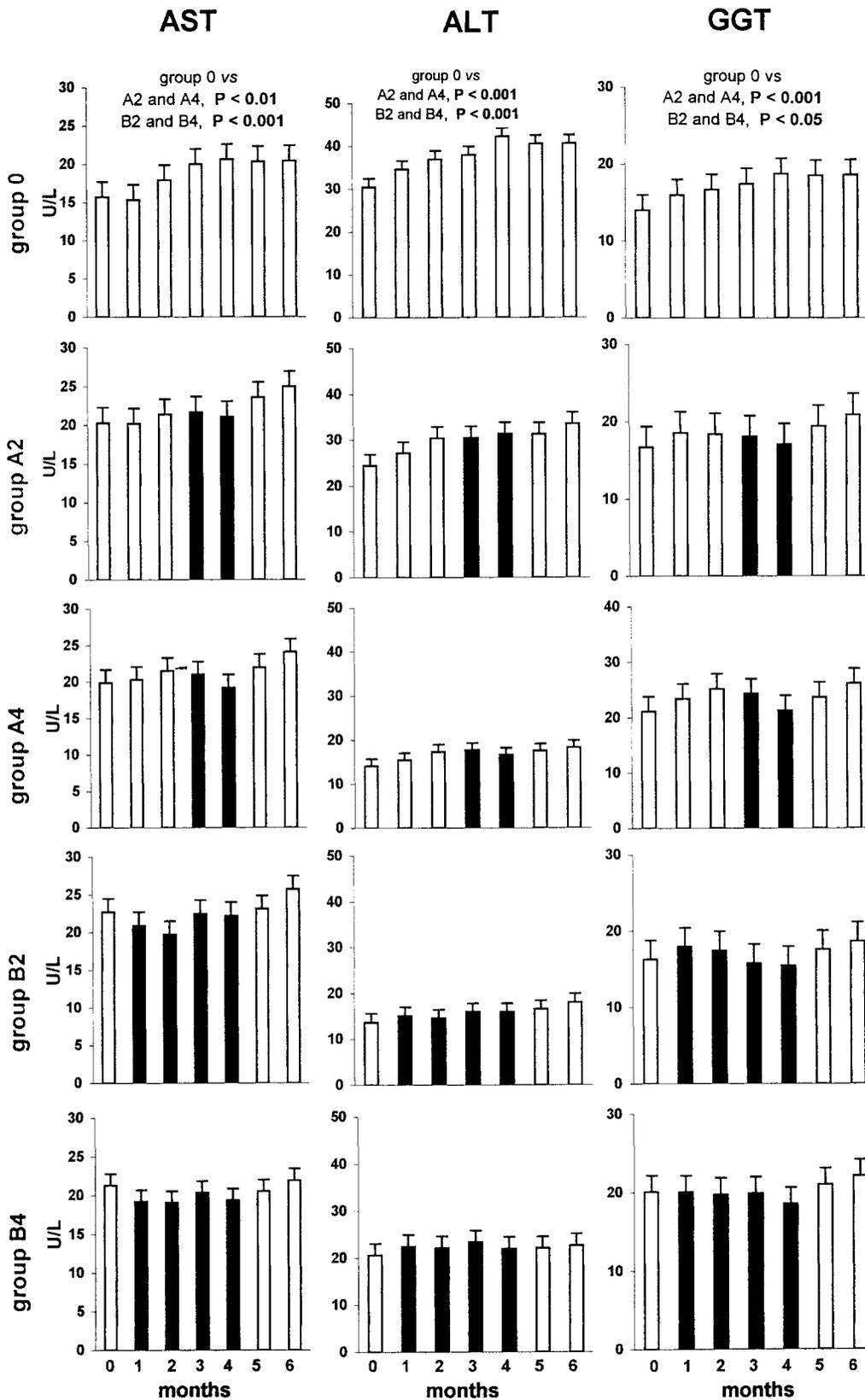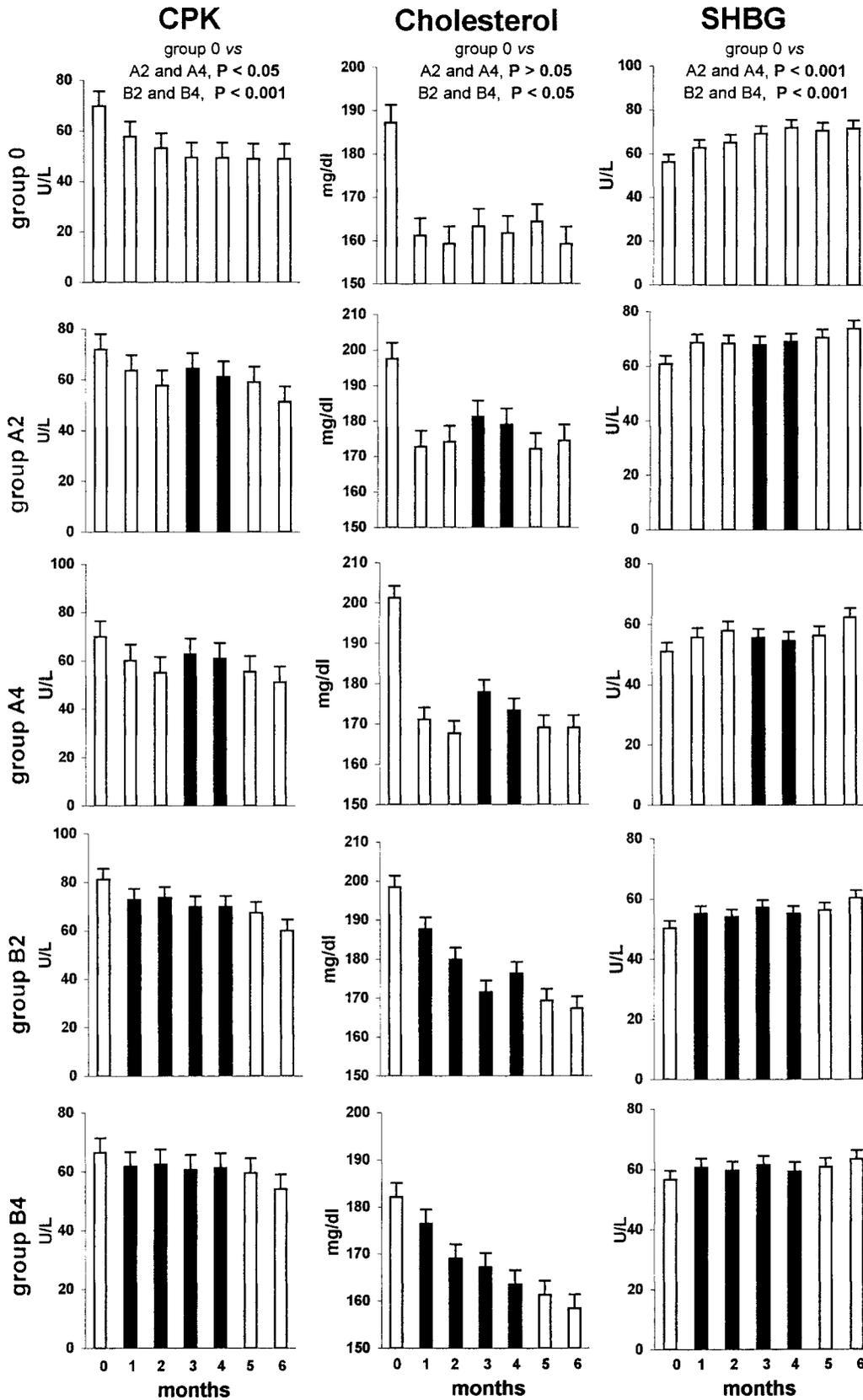
FIG. 6. Variations (mean ± SE) of the three indicated biochemical parameters of thyroid hormone action in the five groups of patients throughout the 6-month duration of the trial. Variations of the remaining six biochemical parameters are illustrated in Figs. 7 and 8. For each biochemical parameters, all data points from 0–6 months in group 0 are compared with all data points in groups A2 and A4 or B2 and B4 by ANOVA, and the resulting *P* value is shown. In each group, the relevant per cent change is summarized in Figs. 9 and 12.

FIG. 7. Variations (mean ± SE) of the three indicated biochemical parameters of thyroid hormone action in the five groups of patients throughout the 6-month duration of the trial. Variations of the remaining six biochemical parameters are illustrated in Figs. 6 and 8. For other details, see legend to Fig. 6. To convert cholesterol from mg/dl to mmol/l, multiply by 0.02586.
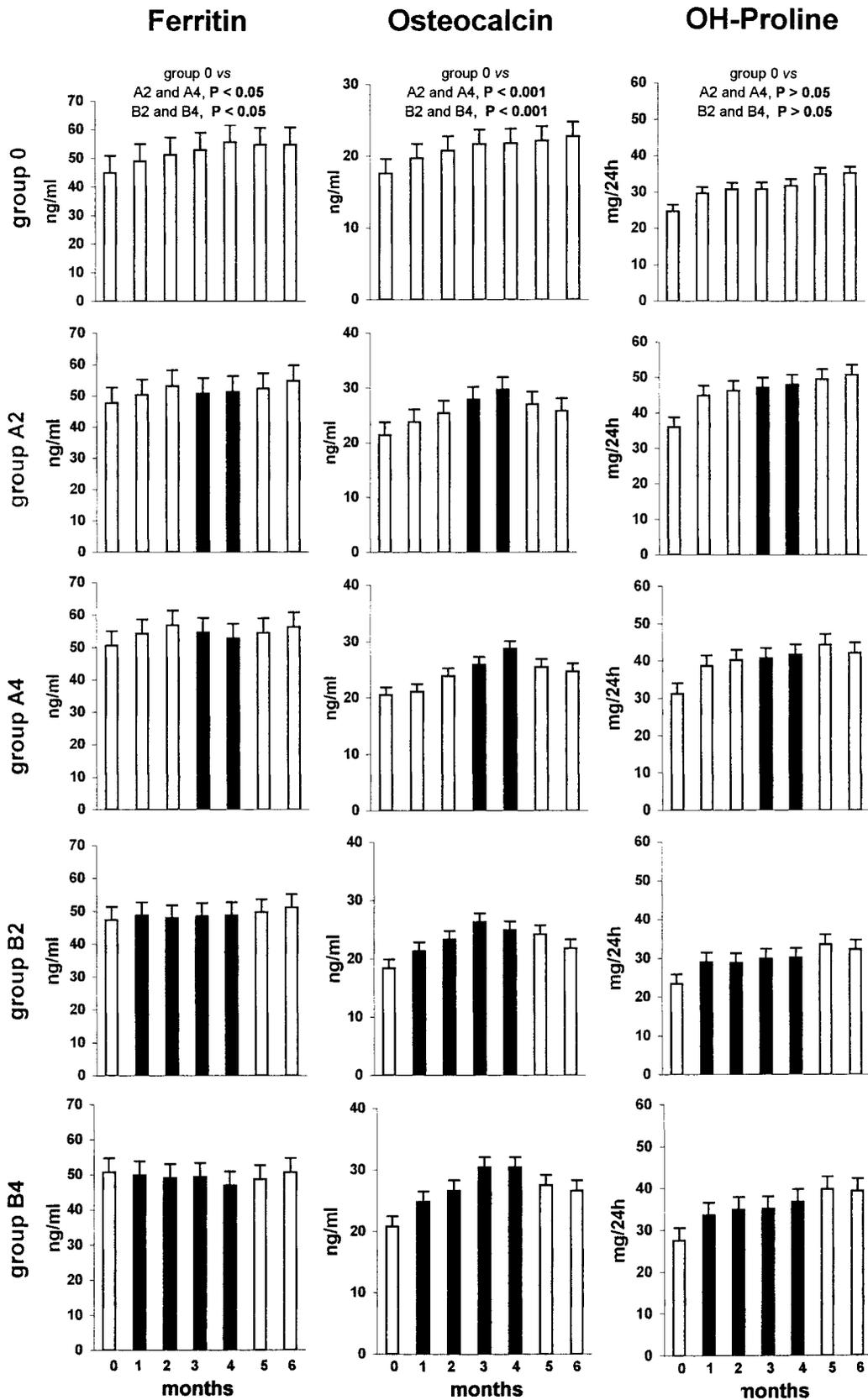
FIG. 8. Variations (mean ± SE) of the three indicated biochemical parameters of thyroid hormone action in the five groups of patients throughout the 6-month duration of the trial. Variations of the remaining six biochemical parameters are illustrated in Figs. 6 and 7. For other details, see legend to Fig. 6. To convert urinary OH-proline from from mg/d to μmol/l, multiply by 7.628.
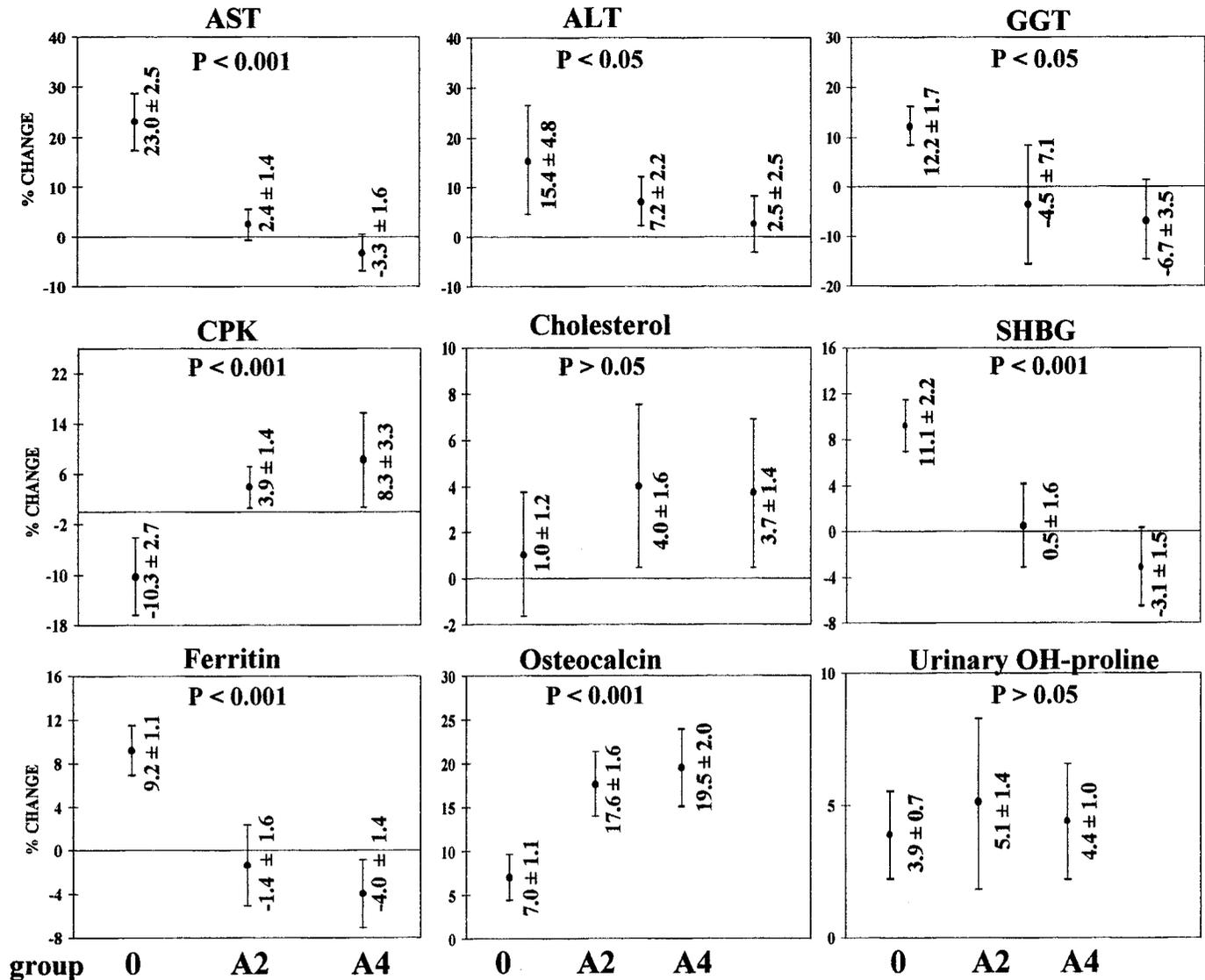
FIG. 9. Mean ± SE percentage changes (calculated as in Fig. 5) and 95% CI of the nine biochemical parameters evaluated in groups 0, A2, and A4. Only changes in cholesterol and urinary OH-proline were not significant ($P > 0.05$) in group 0 *vs.* groups A2 and A4.

12). Except for ferritin ($P < 0.01$) and SHBG ($P < 0.05$), the two doses of carnitine were equally effective (Fig. 12).

Bone densitometry. Because of the small number of subjects, the increase of posttherapy BMD of either lumbar spine or left proximal femur in groups B was not statistically significant ($P > 0.05$) from the corresponding posttherapy changes observed in group 0 *vs.* groups B (Fig. 10). However, when either carnitine group is analyzed separately *vs.* the placebo group, then only the comparison between group B4 and group 0 concerning vertebral BMD resulted statistical significant ($P < 0.05$).

Adverse events

Only during placebo administration, the following events were reported: headache (two group 0 patients, one group A4 patient, and one group B2 patient), pruritus (one group

0 patient). These disturbances were described as moderate and transient.

During carnitine administration, of the 40 persons in groups A and B, only one A2 patient and one B4 patient complained of disturbances. These consisted in nausea and gastralgia, which had appeared during the first week, disappeared within the next one and were minimal, so that carnitine administration was not discontinued. Transient and moderate gastralgia was also reported by one group 0 patient.

Except for the changes described above for the thyroid hormone-sensitive parameters, in none of the 40 subjects there were significant alterations of erythrocyte sedimentation rate, blood counts (RBC, WBC, platelets), serum electrolytes (Na^+, K^+, Ca^{2+}, P^-), serum proteins (including protein electrophoresis), bilirubinemia, creatininemia, glycemia, and urine chemistry.
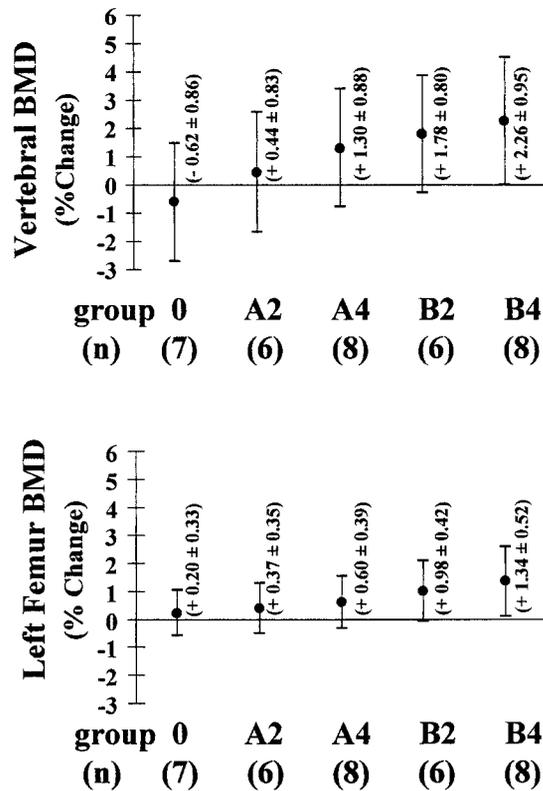
FIG. 10. Changes in BMD (lumbar vertebrae and left femur) at the end of the clinical trial with respect to baseline in the five study groups. Data are presented as 95% CI, with mean ± SE given in *parentheses*. Differences between group 0 *vs.* A2 and A4 or group 0 *vs.* B2 and B4, as analyzed by ANOVA, were not statistically significant. In a par-wise comparison, only group 0 *vs.* group B4 difference in vertebral BMD resulted statistically significant ($P < 0.05$), as also confirmed by two-tailed Student's *t* test.

Discussion

Before us only 11 naturally hyperthyroid patients treated with 1 or 2 g/d carnitine for up to 6 weeks had been evaluated (8, 9, 11). Clinical improvement started from the second week and consisted in the decrease of heart rate, body temperature, asthenia, nervousness, insomnia, hyperreflexia, and tremors. In a 4-wk study on iatrogenic hyperthyroidism (10), six male volunteers who received 100 μg/d L-T$_3$ and 1 g/d carnitine, were compared with six male volunteers who received only L-T$_3$. Unfortunately, results are summarized in a Table where a few parameters are presented (as mean values without SD or SE) in different ways (10), thus making interpretation and comparison with our data impossible. Body weight is reported as mean change, and it was −10.5 lbs (4.7 kg) or −10.4 lbs (−4.7 kg) in the T$_3$ group or T$_3$ plus carnitine group, respectively. Pulse rate is reported as mean final values (98 or 90 bpm, respectively), and serum cholesterol as mean per cent change (−38% or −22%) (10). All these studies (8–11) failed to specify how symptoms were gauged, and all were unblinded and devoid of statistical analysis.

With our protocol, we could evaluate whether carnitine is able to both reverse and prevent (or minimize) iatrogenic hyperthyroidism. In groups A, symptoms/signs that had

worsened while on L-thyroxine plus placebo returned to baseline once placebo had been substituted with carnitine. In groups B, symptoms/signs remained stable or even ameliorated as long as carnitine was associated to L-thyroxine, implying that the carnitine effect prevailed over the T$_4$ effect. The preponderance of the carnitine effect was confirmed by the negative sign of the second over first bimester change in groups A or the first two bimesters over baseline change in groups B that was observed for a number of biochemical parameters: AST, GGT, SHBG, and ferritin. Therefore, our observations confirm the observations of Hellthaler *et al.* (7) in rats, in which administration of L-thyroxine + carnitine caused a 10–50% decrease of AST and ALT, while L-thyroxine administration caused a 30–150% increase.

Three biochemical parameters were spared by the antagonism exerted by carnitine on thyroid hormone action: serum TSH, serum osteocalcin, and urinary OH-P. A fourth parameter, circulating total cholesterol is relatively refractory to carnitine, since only the group B showed a statistical difference ($P < 0.05$) with group 0. The action of carnitine on both TSH (*i.e.* on thyrotrophs) and OH-P (*i.e.* on osteoclasts) was nil, because changes matched those caused by placebo. In contrast, the positive response on osteocalcin was greater than that caused by placebo, indicating a synergistic effect with thyroid hormones. In cell cultures, we observed differences among various cell types, because the inhibition of thyroid hormone nuclear uptake was in hepatocytes greater than in neurons (12). Probably, the inhibition of thyroid hormone nuclear entry caused by carnitine in thyrotrophs and osteoclasts is insignificant. Special studies will be required to address this issue, because there are no data available in the literature concerning the carnitine content and uptake in the pituitary and bone. The same ignorance prevents interpretation of the potentiation of the thyroid hormone action on osteoblasts, as indicated by circulating osteocalcin. However, we do confirm the study of Abdennabi *et al.* (23) in mice. In this study (23), three groups of five adult mice each were tested with placebo or 50 mg/kg or 100 mg/kg body weight oral carnitine for 12 wk. In the last two groups, serum osteocalcin increased by 22% and 60% compared with the placebo group.

Because of the different effect of carnitine on osteoclasts and osteoblasts, we should expect a beneficial effect on bone, although of low magnitude considering the relatively short period of administration of carnitine and the consequent interference with only one bone formation cycle. The beneficial effect of carnitine can be appreciated better in the B groups, because they received carnitine for a longer period compared with the A groups. Even though in groups B the posttreatment BMD was measured at the sixth month, namely 2 months after withdrawal of carnitine, there was an average 1.8% (group B2) and 2.3% (group B4) increment in lumbar spine BMD, and a 1.0% (B2) and 1.3% (B4) increment in femur BMD. These beneficial changes contrasted with the −0.6% and +0.2% changes observed in the placebo group. Because of the short duration of treatment and small number of patients as a result of a dropout, statistically significant ($P < 0.05$) was only the difference in vertebral BMD between group 0 and group B4. Clearly, if the increments of BMD are confirmed on a larger series of patients treated for a longer
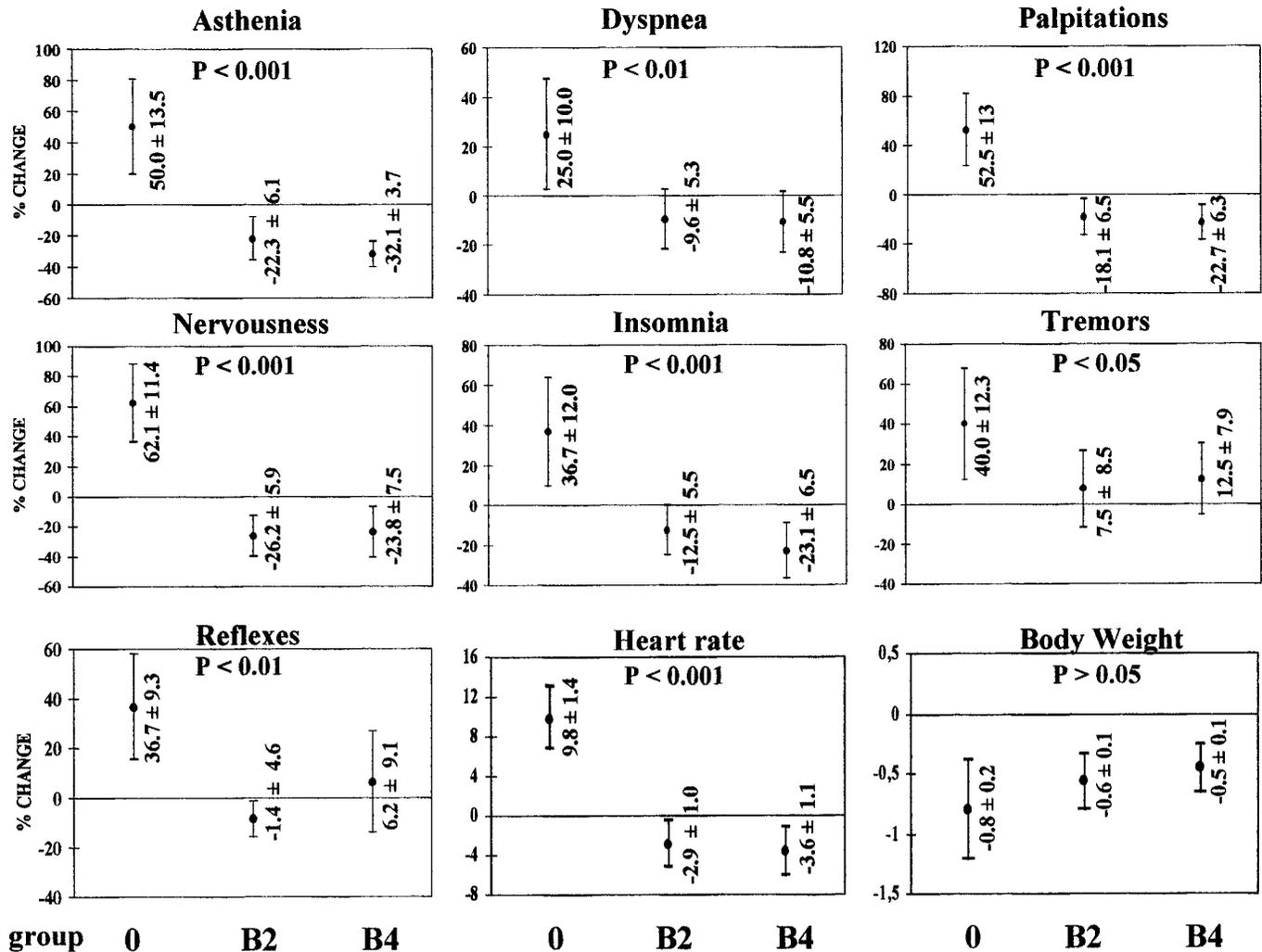
FIG. 11. Mean ± SE percentage change and 95% CI of the nine clinical parameters evaluated in group 0, B2, and B4 patients. Percentage change means the "pooled carnitine value" (*i.e.* score or beats per minutes or kg body weight of the first 4 months) divided by the corresponding baseline (day 0) value, the ratio being multiplied by 100. Only changes in body weight were not significant ($P > 0.05$) in group 0 *vs.* groups B2 or B4.

period of time, the adjunctive carnitine therapy is ideal for postmenopausal women who need to take life-long TSH-suppressive doses of L-thyroxine.

When iatrogenic hyperthyroidism appears, several patients spontaneously reduce the dose of L-thyroxine or take L-thyroxine irregularly or may even stop therapy. In each case, the final result is the absence of consistent suppression of TSH—and this is deleterious in thyroid carcinoma patients. The traditional approach to avoid hyperthyroidism is to individually tailor the dose of L-thyroxine, but this requires frequent clinical and hormone evaluations. (Even by doing so, some patients continue to complain of side effects, because the individual "euthyroid" range is narrower than the population range.) These frequent controls can be eliminated by using a fixed TSH-suppressive daily dose of L-thyroxine plus L-carnitine at 2 g per day or, as preliminary data of ours indicate, even 1 g per day. Alternatively, carnitine can be added only after hyperthyroid symptoms had appeared. After our clinical trial ended and results were known, patients were informed of the cost of carnitine and inquired. Group A and B patients were inquired if they were

willing to continue the adjunctive therapy with 2 g carnitine per day; group 0 patients were asked if they were willing "to take twice daily and orally 2 g of a medication, as natural as thyroxine, that would have protected them from the side-effects of the hormone." The proportion of the favorable responders (34 of 40 or 85% and 8 of 10 or 80%) were similar. When the 42 favorable responders were asked if they preferred to take carnitine for only a strictly limited period of time or for as long as necessary, 33 (79%) preferred the second modality.

On a daily basis, the cost of 1 g carnitine is $0.65, which compares nicely with benzodiazepines (*e.g.* $0.42 to $0.6 for 3 mg bromazepam or 2 mg lorazepam) or β-blockers (*e.g.* $0.1 for 60 mg propanolol), considering that these drugs act on select symptoms and have significant side effects. Other drugs that have been used to counteract hyperthyroidism are bile sequestrants (24–26), the cons of which are the high daily cost ($5 for 8 g cholestyramine or 20 g colestipol), the high frequency of gastrointestinal disturbances, the impaired absorption of fat-soluble vitamins and several drugs, and the main effect being limited to the first week of treatment (26).
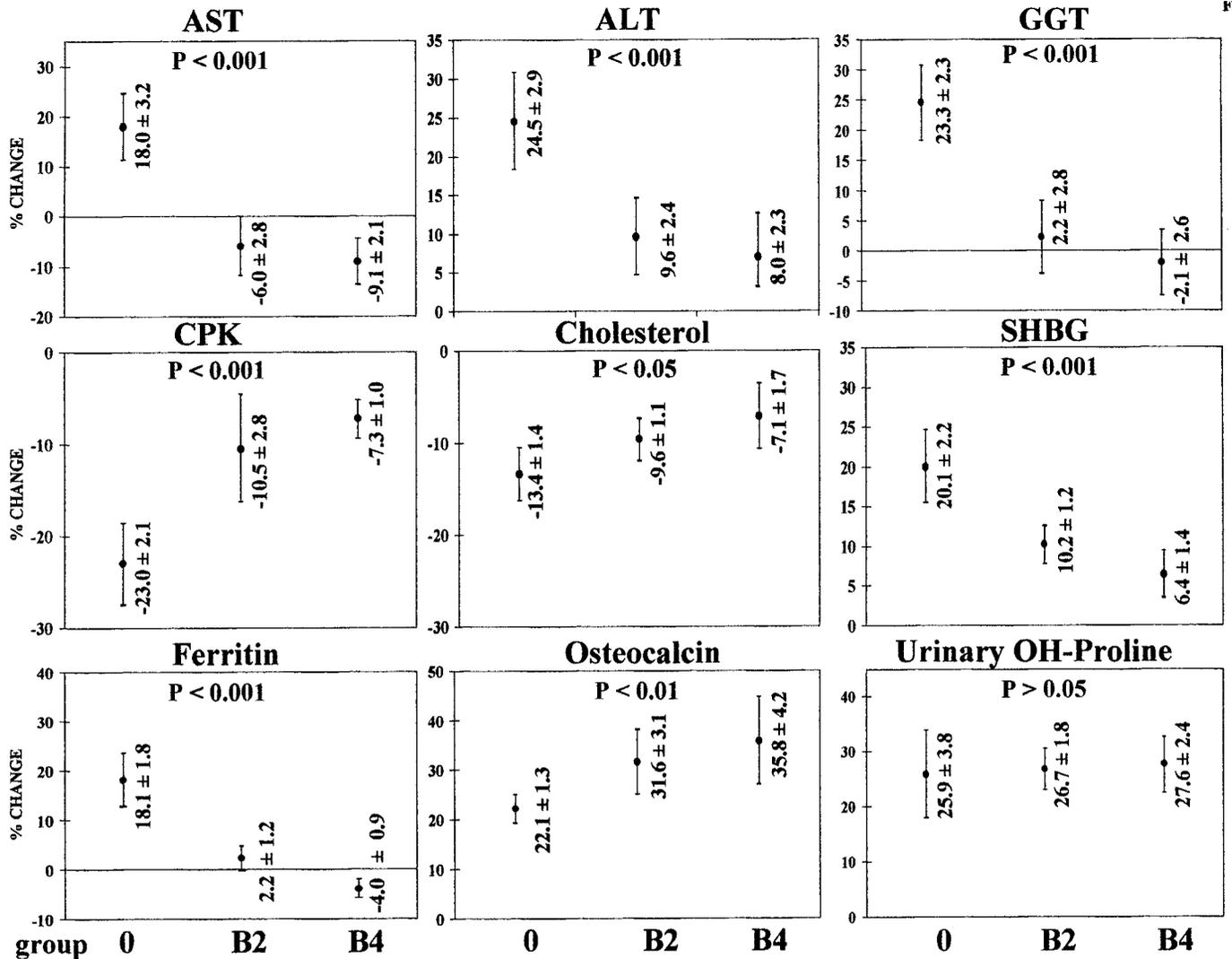
FIG. 12. Mean ± SE percentage changes (calculated as in Fig. 11) and 95% CI of the nine biochemical parameters evaluated in groups 0, B2, and B4 patients. Only changes in urinary OH-proline were not significant in group 0 *vs.* groups B2 and B4.

Theoretically, other drugs that interfere with thyroid hormone either transport accross cells or interaction with nuclear receptors (*e.g.* diphenylhydantoin, nonsteroidal antiinflammatory drugs, amiodarone, *etc.*) (27) might also be used. However, none of all the above drugs is naturally occurring, and each has important side-effects. In sharp contrast, carnitine has no toxicity, teratogenicity, known contraindications, interaction with drugs, or important side effects. In addition, hyperthyroidism impoverishes the tissue deposits of carnitine (28, 29), thus creating a true situation of secondary carnitine deficiency (4). In our group 0 patients, 6 months of L-thyroxine therapy increased the urinary excretion of carnitine by almost 3-fold (Fig. 1), reflecting its thyroid hormone-induced efflux from cells. If we also consider that carnitine inhibits T_3 and T_4 entry into the nucleus of a number of peripheral cells (12), then there is a double rationale for the use of carnitine at least as ancillary therapy of hyperthyroidism: to replenish the tissue deposits and to counteract thyroid hormones in the periphery.

Carnitine could be of particular use when it is important to use the lowest possible dose of antithyroid drugs, such as pregnancy, lactation and liver and/or hematologic disorders (30, 31), since these drugs cross the placenta, are secreted into the milk, and have liver and hematopoietic toxicity (14, 30, 31). Because carnitine crosses the placenta and is devoid of fetal toxicity (32), and because of the difficulties to treat fetal thyrotoxicosis (33)—a serious complication of a number of pregnant women with Graves' disease—carnitine would be an ideal drug in this setting. Also forms of thyrotoxicosis due to leakage of thyroid hormones, or antithyroid drug-resistant thyrotoxicosis (*e.g.* amiodarone-related thyrotoxicosis) or thyroid storm are amenable to treatment with carnitine. Thyroid storm is a serious emergency that has a mortality of 20–50% and which is triggered by precipitating events (34). Thus, carnitine would be useful both for the prevention and the therapy of the thyroid storm.

Acknowledgments

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