

# CARNITINE VERSUS ANDROGEN ADMINISTRATION IN THE TREATMENT OF SEXUAL DYSFUNCTION, DEPRESSED MOOD, AND FATIGUE ASSOCIATED WITH MALE AGING

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## ABSTRACT

**Objectives.** To compare testosterone undecanoate versus propionyl-L-carnitine plus acetyl-L-carnitine and placebo in the treatment of male aging symptoms.

**Methods.** A total of 120 patients were randomized into three groups. The mean patient age was 66 years (range 60 to 74). Group 1 was given testosterone undecanoate 160 mg/day, the second group was given propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day. The third group was given a placebo (starch). Drugs and placebo were given for 6 months. The assessed variables were total prostate-specific antigen, prostate volume, peak systolic velocity, end-diastolic velocity, resistive index of cavernosal penile arteries, nocturnal penile tumescence, total and free testosterone, prolactin, luteinizing hormone, International Index of Erectile Function score, Depression Melancholia Scale score, fatigue scale score, and incidence of side effects. The assessment was performed at intervals before, during, and after therapy.

**Results.** Testosterone and carnitines significantly improved the peak systolic velocity, end-diastolic velocity, resistive index, nocturnal penile tumescence, International Index of Erectile Function score, Depression Melancholia Scale score, and fatigue scale score. Carnitines proved significantly more active than testosterone in improving nocturnal penile tumescence and International Index of Erectile Function score. Testosterone significantly increased the prostate volume and free and total testosterone levels and significantly lowered serum luteinizing hormone; carnitines did not. No drug significantly modified prostate-specific antigen or prolactin. Carnitines and testosterone proved effective for as long as they were administered, with suspension provoking a reversal to baseline values. Only the group 1 prostate volume proved significantly greater than baseline 6 months after testosterone suspension. Placebo administration proved ineffective. Negligible side effects emerged.

**Conclusions.** Testosterone and, especially, carnitines proved to be active drugs for the therapy of symptoms associated with male aging. UROLOGY 63: 641–646, 2004. © 2004 Elsevier Inc.

The controversial concept that male aging symptoms might constitute a “male climacteric” was suggested in 1939.<sup>1</sup> A survey of 1079 men aged 39 to 70 years in the Massachusetts Male

Aging Study revealed that the annual rate of androgen reduction was 1.2% for free testosterone, 1% for albumin-bound testosterone, and 0.4% for total testosterone.<sup>2</sup> Testosterone proved active in the hypothalamic dopaminergic system,<sup>3</sup> testosterone receptors were found at the level of striated skeletal muscles<sup>4</sup> and corpus cavernosum,<sup>5</sup> and testosterone administration was found to enhance sexual potency in aged men.<sup>6</sup> Androgen decline in the aging male, partial androgen deficiency of the aging male, and andropause have been used to define male aging symptoms collectively. Exogenous testosterone has been considered its therapy.<sup>7</sup>

Several aging mechanisms have been proposed to date, whose common pathway is the increase in reactive oxygen species (ROS), membrane damage, and cell death.<sup>4,8</sup> Propionyl-L-carnitine and acetyl-

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L-carnitine proved active for diseases typical of aging (eg, intermittent claudication and Alzheimer's disease) because of their antioxidant activity owing to a Krebs' cycle increase.<sup>9-11</sup> Testosterone increases the carnitine tissue concentration.<sup>11,12</sup> Carnitines are present in the vast majority of mammalian cells in homeostatic equilibrium, and their administration causes minor side effects.<sup>11</sup> Thus, we tested acetyl-L-carnitine/propionyl-L-carnitine administration on male aging symptoms.

## MATERIAL AND METHODS

The Società Italiana di Studi di Medicina della Riproduzione ethical committee approved this research, and patients were informed that they might receive a placebo.

The inclusion criteria<sup>7</sup> were as follows: patients older than 60 years whose chief complaints were symptoms within the working definition of androgen decline in the aging male proposed by the International Society for the Study of the Aging Male.<sup>7</sup> These symptoms included decreased libido and erectile quality, depressed mood and intellectual concentration ability, irritability, fatigue, and free testosterone lower than 6 pg/mL. A total of 224 patients were considered from January 2, 2002 to June 30, 2002.

The exclusion criteria<sup>7</sup> included lower urinary tract obstructive symptoms, prostate volume greater than 20 cm<sup>3</sup> at suprapubic echography, increased prostate-specific antigen (PSA) level or area suspicious for cancer on prostate digital rectal examination (27 patients), alcohol or cigarette consumption (12 patients), fewer than 6 months after myocardial infarction or major surgery (16 patients), diabetes (12 patients), untreated hypertension, cardiovascular disease (4 patients), neoplastic disease (2 patients), ongoing psychological/pharmacologic or antineoplastic therapy (3 patients), and increased prolactin serum level (no patients).

We enrolled 150 patients in the study; 20 subjects dropped out; and 130 subjects completed the protocol. The patients who withdrew were interviewed by telephone to ascertain the causes. Three patients indicated they did not get any benefit and refused to continue, 5 indicated they felt sufficiently better to discontinue, and 12 patients did not agree with the research because they had been informed they might have received a placebo. Their data were not used.

The patients were randomized into three groups. The first group (40 patients, mean age 64 years, range 60 to 72) used testosterone undecanoate 160 mg/day. The second group (45 patients, mean age 66 years, range 61 to 73) used propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day. The third group (45 patients, mean age 63 years, range 61 to 74) received placebo (one 500-mg starch tablet/day). The drugs and placebo were given for 6 months, delivered by nurses unaware of the randomization group in anonymous color-coded boxes whose contents were disclosed at the end of the research.

### DATA COLLECTION

The medical history was collected and the following variables were assessed for each patient before, during (3 and 6 months), and 6 months after therapy: total PSA, prostate volume, peak systolic velocity (PSV), end-diastolic velocity (EDV), resistive index (RI), nocturnal penile tumescence (NPT), total and free testosterone, luteinizing hormone (LH), and prolactin.

The total PSA blood concentration was tested with a monoclonal antibody automated assay.<sup>13</sup> The prostate volume was evaluated with suprapubic echography and the calculation of the three diameters.<sup>13</sup> The PSV, EDV, and RI

[RI = (PSV - EDV/EDV) × 100] of the left and right cavernosal arteries were assayed with dynamic echo-color Doppler of the penis after intracavernosal injection of 10 µg prostaglandin E<sub>1</sub>.<sup>14</sup>

NPT recording was performed with the RigiScan (Dacomed, Minneapolis, Minn). A rigidity increase compared with the baseline value of greater than 70% at the base of the penis and greater than 60% at the top and a circumference increase greater than 2 cm at the top of the penis and greater than 3 cm at the base was considered a full erection. The total duration in minutes of a 3-night full erection recording period was recorded.<sup>14</sup>

Blood samples for total (normal range 8.4 to 28.7 nmol/L) and free (normal range 8.7 to 54.7 pg/mL) testosterone, LH, and prolactin were drawn from each patient between 8:00 and 8:30 AM (90 to 120 minutes after the morning drug administration). Total testosterone was measured by recombinant immunoassay after extraction and celite chromatography. The intra-assay and interassay coefficient of variation was 6% and 13.5%, respectively. The assay does not cross-react with methyl-testosterone. Free testosterone was calculated as the product of the total and percentage of dialyzable free testosterone.<sup>15</sup> The intra-assay and interassay coefficient of variation was 5% and 6.6%, respectively. The reagents were from Diagnostic Products (Los Angeles, Calif).

Sexual function was assessed with the five domains version of the International Index of Erectile Function (IIEF-15)<sup>16</sup>: erectile function (items 1 to 5 and 16), sexual intercourse satisfaction (items 6 to 8), orgasm (items 9 to 10), sexual desire (items 11 and 12), and general sexual well-being (items 13 and 14). The men's mood level was assessed with the Hamilton Depression and Melancholia Scale<sup>17</sup> and fatigue with a fatigue scale.<sup>18</sup> The score for each patient was calculated.

At each data collection, the patients underwent psychosexual counseling and digital rectal examination of the prostate.

### STATISTICAL ANALYSIS

PSA, prostate volume, PSV, EDV, RI, NPT, total and free testosterone, prolactin, and LH data were compared within groups by randomized block (1 patient = 1 block) analysis of variance and among the groups by analysis of variance. Natural data were used, with the exception of RI whose data were transformed ( $\sin^{-1} \sqrt{p/100}$ , where p is percent value). Psychometric tests and fatigue scale scores were compared within and among the groups by the Friedman test. Side effects were compared with chi-square test.<sup>19</sup>

## RESULTS

The results are presented in Table I. No statistically significant differences were observed in the mean age or baseline values in each patient group. It could be argued that the outcomes were not influenced by these variables. Placebo administration did not lead to any statistically significant differences.

Drug administration did not modify the PSA level significantly. Group 1 displayed a statistically significant increase in prostate volume at 3 months (F = 11.2; P < 0.01) and 6 months (F = 9.4; P < 0.01). Six months after suspension, the prostate volume had diminished significantly (F = 12.455; P < 0.01), but was significantly greater (F = 4.732; P < 0.05) than baseline. Group 2 did not show any changes in prostate volume (F < 1).

**TABLE I. Results of assessed variables in three groups\***

Variable	Before Therapy			During Therapy (3 mo)			End of Therapy (6 mo)			6 mo After Therapy		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
PSA (ng/mL)	2.0 ± 0.7	2.4 ± 0.9	1.8 ± 0.8	2.0 ± 0.8	2.2 ± 0.7	1.8 ± 0.8	2.0 ± 0.9	2.3 ± 0.8	1.8 ± 0.8	2.0 ± 0.7	2.2 ± 0.9	2.0 ± 0.9
PV (cm <sup>3</sup> )	15.3 ± 2.8	15.2 ± 2.7	15.6 ± 3.2	18.9 ± 3.0	14.5 ± 2.6	15.5 ± 3.4	25.4 ± 2.6	15.1 ± 3.1	15.6 ± 3.3	18.4 ± 2.8	15.1 ± 3.1	15.6 ± 3.3
PSV (cm/s)	30.2 ± 3.8	30.8 ± 4.2	30.7 ± 3.7	35.9 ± 3.2	38.9 ± 3.1	31.9 ± 3.2	36.7 ± 4.3	39.9 ± 5.0	31.8 ± 4.7	31.7 ± 5.3	31.9 ± 4.0	31.8 ± 6.7
EDV (cm/s)	14.1 ± 5.1	13.7 ± 6.3	14.0 ± 5.6	6.8 ± 3.6	5.0 ± 3.8	13.8 ± 3.6	6.5 ± 3.7	4.7 ± 4.0	12.7 ± 4.2	13.9 ± 4.2	13.1 ± 5.9	13.7 ± 6.0
RI (%)	46.9 ± 4.3	48.2 ± 4.4	47.5 ± 5.2	64.2 ± 4.3	69.0 ± 5.2	51.4 ± 4.3	65.2 ± 4.5	70.0 ± 4.5	51.9 ± 4.7	46.7 ± 6.2	48.3 ± 5.9	49.0 ± 7.0
NPT (min)	83 ± 19	83 ± 18	83 ± 21	123 ± 21	156 ± 16	86 ± 21	120 ± 26	158 ± 28	88 ± 23	87 ± 21	85 ± 23	87 ± 19
TT (nmol/L)	9.89 ± 1.84	10.83 ± 1.86	10.53 ± 2.11	11.28 ± 1.61	10.76 ± 2.12	11.27 ± 2.11	13.96 ± 2.81	11.96 ± 2.66	10.26 ± 2.28	10.00 ± 2.21	10.66 ± 1.75	10.42 ± 1.93
FT (pg/mL)	4.4 ± 0.8	4.9 ± 0.9	4.2 ± 0.6	22.5 ± 4.2	4.7 ± 1.0	4.2 ± 0.7	23.7 ± 4.0	4.7 ± 0.8	4.1 ± 0.7	4.2 ± 0.7	4.5 ± 0.6	4.7 ± 0.5
LH (IU/L)	8.8 ± 0.6	8.4 ± 0.8	8.5 ± 0.6	4.3 ± 0.6	8.5 ± 0.8	8.6 ± 0.6	4.2 ± 1.2	8.5 ± 0.6	8.7 ± 0.4	8.6 ± 0.8	9.0 ± 0.7	8.9 ± 0.5
PRL (μg/mL)	7.6 ± 1.9	7.4 ± 1.9	7.5 ± 2.1	7.7 ± 1.5	7.4 ± 1.6	7.3 ± 1.7	7.4 ± 1.6	7.7 ± 1.6	7.3 ± 1.7	7.7 ± 1.6	7.8 ± 1.2	7.9 ± 1.1
IIEF-15												
domain score												
Erectile function	8 (5–19)	8 (5–22)	8 (5–21)	15 (6–23)	18 (7–28)	9 (6–22)	16 (6–29)	24 (8–29)	9 (6–22)	8 (5–18)	8 (5–22)	9 (6–22)
Sexual intercourse satisfaction	4 (3–6)	4 (3–7)	4 (2–5)	5 (4–6)	5 (4–7)	4 (3–6)	5 (3–10)	6 (3–10)	4 (3–5)	4 (3–6)	4 (3–7)	4 (3–5)
Orgasm	3 (1–5)	3 (2–6)	3 (2–4)	4 (3–6)	5 (3–8)	3 (2–5)	4 (3–9)	7 (3–10)	3 (2–4)	3 (1–5)	3 (2–6)	3 (2–4)
Sexual desire	4 (3–6)	4 (3–5)	3 (3–5)	6 (4–7)	6 (4–8)	3 (3–5)	7 (6–9)	7 (4–10)	3 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)
General sexual well-being	3 (2–4)	3 (2–4)	3 (2–4)	4 (2–6)	5 (3–7)	3 (2–4)	4 (2–9)	6 (4–10)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)
DMSIII score	7 (5–8)	7 (5–8)	7 (5–8)	5 (3–6)	3 (2–6)	7 (5–8)	5 (3–6)	3 (2–6)	7 (5–8)	7 (4–9)	7 (4–9)	7 (4–9)
FS score	3 (1–6)	3 (1–5)	3 (1–4)	0 (0–3)	1 (0–4)	3 (2–5)	1 (0–4)	0 (0–2)	3 (2–5)	3 (1–6)	3 (1–5)	3 (1–4)

KEY: PSA = prostate-specific antigen; PV = prostate volume; PSV = peak systolic velocity; EDV = end-diastolic velocity; RI = resistive index (of right cavernosal artery); NPT = nocturnal penile tumescence (3-night full erection duration); TT = total testosterone; FT = free testosterone; LH = luteinizing hormone; PRL = prolactin; IIEF-15 = International Index of Erectile Function; DMSIII = Hamilton Depression and Melancholia Scale; FS = fatigue scale.

Data presented as mean ± SD, with exception of IIEF, DMSIII, and FS scores, which are presented as median, with the range in parentheses.

Data used were natural, with exception of RI, which used angular transformed data.

\* Group 1, testosterone undecanoate (160 mg/day); group 2, propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day; and group 3, placebo.

Testosterone and carnitine suspension provoked a return to baseline of the group 1 and 2 variables that had been significantly modified during therapy. Only the right cavernosal artery data are presented, because the left cavernosal artery data proved similar. Group 1 had a statistically significant increase in PSV and RI and a statistically significant decrease in EDV at 3 months ( $F = 11.342$ ,  $F = 15.226$ , and  $F = 14.120$ , respectively;  $P < 0.01$ ) but not at 6 months ( $F < 1$ ,  $F = 1.149$ , and  $F = 1.123$ , respectively). Group 2 had similar results. No statistically significant differences occurred between 3 or 6 months in groups 1 and 2 ( $F = 1.089$  and  $F = 1.119$ , respectively).

Carnitine and testosterone administration produced a statistically significant increase in NPT at 3 months ( $F = 19.050$  and  $F = 12.381$ , respectively;  $P < 0.01$ ), which were not significantly different at 6 months ( $F < 1$ ). The 3-month and 6-month carnitine NPT periods proved significantly longer than those after administration of testosterone ( $F = 8.210$  and  $F = 7.550$ , respectively;  $P < 0.01$ ).

Carnitines did not significantly modify the hormonal levels ( $F < 1$ ). Oral testosterone induced a statistically significant increase in the total and free testosterone concentration at 3 months ( $F = 167.14$ ,  $P < 0.01$ , and  $F = 4.566$ ,  $P < 0.05$ , respectively) but not at 6 months ( $F < 1$  and  $F = 1.550$ , respectively). It also induced a statistically significant decrease in the LH serum concentration at 3 months ( $F = 229.37$ ,  $P < 0.01$ ) but not at 6 months ( $F < 1$ ). Testosterone administration did not modify the prolactin concentration significantly ( $F < 1$ ).

In group 1, the erectile function and sexual desire IIEF-15 domain scores were significantly increased at 3 months ( $q = 21.18$  and  $q = 19.27$ , respectively;  $P < 0.01$ ), with the former increased significantly at 6 months ( $q = 23.71$ ;  $P < 0.01$ ) and the latter not ( $q = 2.45$ ). Sexual intercourse satisfaction had increased significantly at 6 months ( $q = 19.23$ ;  $P < 0.01$ ) but not at 3 months ( $q = 3.29$ ). The general sexual well-being and orgasm domain changes were never statistically significant ( $q = 1.19$ ,  $q = 2.17$ ,  $q = 1.81$ ,  $q = 2.21$ , respectively).

In group 2, IIEF-15 erectile function, orgasm, sexual desire, and general sexual well-being domain scores had significantly increased at 3 months ( $q = 29.17$ ,  $q = 19.02$ ,  $q = 21.01$ ,  $q = 20.19$ , respectively;  $P < 0.01$ ). Erectile function and orgasm had increased significantly at 6 months ( $q = 29.11$  and  $q = 19.11$ , respectively;  $P < 0.01$ ), but sexual desire and general well-being did not ( $q = 2.02$  and  $q = 2.90$ , respectively). Sexual intercourse satisfaction had significantly increased at 6 months ( $q = 19.02$ ;  $P < 0.01$ ) but not at 3 months ( $q = 2.18$ ;  $P =$  not significant). The following carnitine scores were significantly greater than the

testosterone scores: the 3-month ( $q = 14.56$ ;  $P < 0.05$ ) and 6-month ( $q = 22.19$ ;  $P < 0.01$ ) erectile function domain; the 6-month orgasm domain ( $q = 18.53$ ;  $P < 0.01$ ); and the 6-month general sexual well-being domain ( $q = 19.54$ ;  $P < 0.01$ ). The other IIEF-15 scores were not significantly different from those with testosterone administration. Carnitine and testosterone administration significantly lowered the Hamilton Depression and Melancholia Scale score at 3 months ( $q = 37.547$  and  $q = 18.001$ , respectively;  $P < 0.01$ ) but not at 6 months ( $q = 1.131$  and  $q = 2.765$ , respectively). The 3-month and 6-month carnitine Hamilton Depression and Melancholia Scale score proved significantly lower than the score with testosterone ( $q = 27.115$  and  $q = 29.231$ , respectively;  $P < 0.01$ ). Testosterone and carnitine administration significantly diminished the fatigue scale score at 3 months ( $q = 33.440$  and  $q = 53.806$ , respectively;  $P < 0.01$ ) and 6 months ( $q = 41.390$  and  $q = 44.310$ , respectively). No statistically significant differences emerged between the group 1 and 2 scores ( $q = 2.112$  and  $q = 2.119$ ).

The psychometric test and fatigue scale data were confirmed by psychosexual counseling sessions.

The occurrence of side effects proved negligible with no statistically significant differences found among the three patient groups. In no patient was therapy suspended. One group 1 patient and one group 3 patient reported mild epigastralgia, and one group 2 patient reported mild headache (chi-square  $< 1$ ).

## COMMENT

Vitamin E, tocopherol, glutathione (conventional anti-ROS drugs) interact directly with the substrate and decrease ROS independent of their concentration.<sup>20</sup> Carnitines restore the ROS physiologic concentration by acting on the Krebs cycle.<sup>10,11</sup> ROS are physiologic substances whose concentration is critical to preserving membrane elasticity.<sup>11</sup> Increased ROS have been found in Peyronie's disease<sup>21</sup> and in idiopathic<sup>22</sup> and postinflammatory<sup>23</sup> male oligoasthenospermia. "Conventional" anti-ROS were ineffective in these cases, and carnitine administration proved active. Their different mechanisms of action may explain the differences in effectiveness.<sup>21-23</sup> Aged men display increased ROS, but conventional anti-ROS are considered inactive in androgen decline in treating the aging male symptoms.<sup>8</sup> Carnitines have not been used until now.

The data of the patients who withdrew from the study were excluded, even though it is customary to include them (intention to treat analysis), because inclusion would have impaired the control of population heterogeneity,<sup>24</sup> which requires the pa-

tients to be the same in the examined classes to use randomized block analysis of variance.<sup>19</sup> A survey indicated that inclusion of the “drop-out” data did not modify the statistical significance of the outcomes. A standard questionnaire for aging men was not used, because we preferred to discriminate the best drug activities on the different symptoms of aging. We adopted the five domain version of the IIEF-15 questionnaire for the same reason.

Among the different types of testosterone preparations, testosterone undecanoate was preferred according to published reports.<sup>6,7</sup> The carnitine and testosterone doses were selected from preliminary assessments using 1, 2, and 3 g/day for each carnitine and 80, 120, 160, and 200 mg/day for testosterone. In these studies, 2 g/day of each carnitine and 160 mg/day of testosterone was as effective as 3 g/day and 200 mg/day, respectively, but were expected to induce fewer side effects. These doses proved consistent with published reports<sup>6,7,9,10</sup> and the manufacturers' instructions.

Baseline PSA and prostate volume were not significantly modified by the carnitine administration. Testosterone administration significantly increased the prostate volume (but not the PSA level) to more than 20 cm<sup>3</sup> at 6 months, confirming published reports.<sup>8,14</sup> Thus, the study was terminated, even though no patient displayed any prostatic symptoms. The group 1 prostate volume had not reverted to baseline 6 months after testosterone suspension, even though the mean volume became less than 20 cm<sup>3</sup>. No area suspicious for cancer was found by digital rectal examination. As of June 15, 2003, the prostate volume had not decreased further. The PSA value did not increase nor was an area suspicious for cancer found at digital rectal examination.

Testosterone and carnitines (but not placebo) increased the PSV and RI equally and lowered the EDV of the cavernosal arteries. Testosterone improved sexual potency and echo-color Doppler spectral traces and proved active in the nitric oxide endothelial and neuronal penile system, with a positive relationship between the severity of erectile failure and the amount of androgen deficiency.<sup>25,26</sup> The mechanism by which testosterone administration lowers the EDV is unknown. Increased PSV lowered the EDV, spreading albuginea, and thus enhancing its occlusive mechanism on the sinusoidal emissary veins.<sup>8,14</sup> Direct testosterone activity on albuginea cannot be ruled out, because receptors were found in the corpus cavernosum and apoptosis and vascular and tissue degeneration are patterns of testosterone deficiency.<sup>5</sup> Propionyl-L-carnitine has been registered in Italy for intermittent claudication. Circulation was improved using an endothelial-dependent substance (probably prostaglandin E<sub>1</sub>), with a detectable modification on echo-color Doppler examina-

tion of lower limb vessels.<sup>9</sup> Again, the mechanism by which carnitines lower EDV is obscure. Increased PSV may be a satellite effect, but a direct effect on albuginea cannot be ruled out. Aged men substitute elastic and muscular tissue with collagen in Buck's fascia and on the sinusoid wall,<sup>14,27</sup> thus resembling a degenerative disease. Carnitines proved active in a variety of degenerative diseases.<sup>9-11</sup>

Testosterone and carnitines increased the IIEF-15 score and NPT significantly, consistent with arterial data. Carnitines proved significantly more active than testosterone in both cases, even if the echo-color Doppler traces proved similar to those after testosterone administration. NPT is currently recorded by measuring the penile increase in diameter and the radial rigidity with the RigiScan. A depressed mood negatively influenced NPT quality, and successful antidepressant therapy restored NPT.<sup>28</sup> We enrolled men whose depressed mood improved during the course of therapy to a greater extent using carnitines than testosterone, thereby explaining the greater activity of carnitines on NPT and the IIEF-15 score. Psychosexual counseling sessions confirmed the psychometric testing results. Testosterone receptors have been found on the third ventricle floor, the preoptic area-anterior hypothalamus, and the amygdala, areas deemed to control sexual and emotional behavior and to influence the paleocortex directly or indirectly by the ascending reticular system.<sup>29</sup> Acetyl-L-carnitine has been shown to preserve the lipid structure of the neuronal membranes and improve the nerve conduction velocity to the extent of restoring electroencephalographic theta waves and increasing cognitive abilities in early Alzheimer's disease.<sup>10</sup>

The fatigue scale score was equally increased by testosterone and carnitines. Testosterone receptors have been proved to exist within skeletal muscle cell cytosol, which increases DNA and protein synthesis and respiration.<sup>4</sup> Carnitines boost the increase and transport of acetyl groups, thereby enhancing Krebs cycle and aerobic metabolism.<sup>11</sup>

Testosterone administration significantly increased free and total testosterone levels and significantly lowered LH; it did not affect the prolactin concentration. These observations are consistent with those of published reports<sup>6,7</sup> and offer evidence that male aging symptoms are linked to blood androgen concentrations and that androgen supplementation might be a successful therapy. In contrast, carnitines did not significantly modify these hormone concentrations but proved even more active than testosterone.

Male and female sex hormones increase L-carnitine levels, carnitine-acetyl-transferase activity in tissues, the synthesis of transcription rates, and the activities of mitochondrial carnitine palmitoyl-transferases and octanoic-transferases,<sup>30</sup> thereby explaining the carnitine activity in hypogonadal

aged men. In humans and experimental models, carnitines have several activities that might influence aging. Fatty acid peroxidation proved depleted, and carnitines restored the phospholipid composition of mitochondrial membranes and enhanced the cellular energetics in mitochondria, increasing cytoplasmic acetyl-coenzyme A concentrations through the higher availability of acetyl groups. In addition, carnitines stabilized cell membrane fluidity by regulating phospholipid levels and reduced ceramide production and insulin-like growth factor, preventing cellular death and apoptosis.<sup>11</sup>

Carnitines had more positive effects than testosterone on NPT, the IIEF-15 erectile function, orgasm, and sexual general well-being domains, and the Hamilton Depression and Melancholia Scale score (ie, in improving erection quality, sexual life, and mood level) in hypogonadal aging men, without increasing hormonal levels. These findings mean that even though the carnitine tissue concentration might also be influenced by sex hormones, the positive activity of carnitine on some male aging symptoms is not strictly linked to sex hormone blood levels. Therefore, at least one side effect of testosterone administration (ie, prostate enlargement) will be avoided by carnitine administration. Our final concern is to not focus solely on androgenic supplementation for male aging therapy, because the results of this study demonstrated that alternative drugs might prove effective.

#### REFERENCES

1. Wermer AA: The male climacteric. *JAMA* 112: 1441–1443, 1939.
2. Gray A, Feldmann A, and McKinlay JB: Age, disease, and changing sex hormone levels in middle aged men: results of the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 73: 1016–1125, 1991.
3. Heaton JP, and Varrin SJ: Effects of castration and exogenous testosterone supplementation in animal model of penile erection. *J Urol* 151: 797–800, 1994.
4. Campbell NC: *Biology*, 3rd ed. New York, Benjamin Cummings Publishing, 1995.
5. Baba K, and Iwamoto T: Delayed testosterone replacement restores nitric oxide synthetase-containing nerve fibres and erectile response in rat penis. *BJU Int* 85: 953–957, 2000.
6. Basaria S, and Dobs AS: Hypogonadism and androgen replacement therapy in the elderly men. *Am J Med* 110: 563–571, 2001.
7. Morales A, and Lunenfeld B: Standards, guidelines and recommendations of the International Society for the Study of the Aging Male (ISSAM): androgen replacement therapy in aging men with secondary hypogonadism—draft of recommendations for endorsement by ISSAM. *Aging Male* 4: 151–162, 2001.
8. Kirby RS, Kirby MG, and Farahd RN: *Men's Health*. Sedgefield, United Kingdom, Atlas Medical Publishing, 2001.
9. Brevetti G, Perna S, Sabbà C, *et al*: Propionyl-L-carnitine in intermittent claudication: double blind, placebo controlled, dose titration, multicenter study. *J Am Coll Cardiol* 26: 1441–1446, 1995.

10. Bonavita E: Study of efficacy and tolerability of acetyl-L-carnitine in senile brain. *Int J Pharm Ther Toxicol* 24: 511–516, 1986.
11. Furlong JH: Acetyl-L-carnitine metabolism and applications in clinical practice. *Alternat Med Rev* 1: 85–92, 1996.
12. Bidzinska B, Petraglia F, Angioni S, *et al*: Effect of different chronic intermittent stressors and acetyl-L-carnitine on hypothalamic beta-endorphin and GnRH and on plasma testosterone levels in male rats. *Neuroendocrinology* 57: 985–990, 1993.
13. Rigatti P, and Scattoni V: *PSA antigene prostatico specifico*. Pavia, Edizioni Medico Scientifiche, 1997.
14. Carson C, Kirby R, and Goldstein I: *Textbook of Erectile Dysfunction*. Oxford, Isis Medical Media, 1999.
15. Vermeulen A: The hormonal activity of post-menopausal ovary. *J Clin Endocrinol Metab* 42: 247–253, 1976.
16. Rosen RC, Riley A, Wagner G, *et al*: The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 49: 822–830, 1997.
17. Bech P, Kastrup M, and Rafaelsen OJ: Minicompendium of evaluation scales for anxiety, depression, mania, schizophrenia, with DSM III correspondent syndromes. *Acta Psychiatrica Scand* 73(suppl): 1–28, 1984.
18. Hwang SS, Chang VT, Cogswell J, *et al*: Clinical relevance of fatigue levels in cancer patients at a Veterans Administration Medical Center. *Cancer* 94: 2481–2489, 2002.
19. Camussi A, Moller F, Ottaviano E, *et al*: *Metodi Statistici per la Sperimentazione Biologica*, 2nd ed. Bologna, Zanichelli, 1995.
20. Comhaire FH, Cristophe AB, Zalata AA, *et al*: The effects of combined conventional treatment, oral antioxidants and essential fatty acids on sperm biology in subfertile men. *Prostaglandins Leukot Essent Fatty Acid* 6: 159–165, 2000.
21. Cavallini G, Biagiotti G, Koverech A, *et al*: Oral propionyl-L-carnitine associated to intraplaque verapamil in the therapy of advanced and resistant Peyronie's disease. *BJU Int* 89: 895–900, 2002.
22. Lenzi A, Lombardo F, Sgrò P, *et al*: Use of carnitine therapy in selected cases of male factor infertility: a double blind cross over trial. *Fertil Steril* 79: 292–300, 2003.
23. Vicari E, and Calogero AE: Effects of treatment with carnitines in infertile patients with prostatitis-epididymitis. *Hum Reprod* 16: 2338–2342, 2001.
24. Collins R, Peto R, Gray R, *et al*: Large-scale randomized evidence: trials and overviews, in Weatherhall DJ, Ledingham JGG, Warrel DA (Eds): *Oxford Textbook of Medicine*, 3rd ed. Oxford, Oxford University Press, 1996, pp 21–32.
25. Mills TM, Lewis RW, and Stopper VS: Androgenic maintenance of inflow and venoocclusion during erection in rat. *Biol Reprod* 59: 1413–1418, 1998.
26. Shasig R, Raymond JF, Olsson CA, *et al*: Androgen induction of DNA synthesis in the rat penis. *Urology* 52: 723–728, 1998.
27. Malourov D, Petrake C, and Costantinidis E: The contribution of cavernous body biopsy in the diagnosis and treatment of male impotence. *Histol Histopathol* 9: 427–431, 1994.
28. Thase ME, Reynolds CF, Jennings JF, *et al*: Diminished nocturnal penile tumescence in depression: a replication study. *Biol Psychiatry* 31: 1136–1142, 1992.
29. Alexander GM, Swerdloff RS, Wang C, *et al*: Androgen behavior correlation in hypogonadal and eugonadal men: cognitive abilities. *Horm Behav* 33: 85–88, 1988.
30. Chiu MK, Schmidt MJ, Shug AL, *et al*: Effect of dehydroepiandrosterone sulfate on carnitine acetyl transferase and L-carnitine levels in oophorectomized rats. *Biochem Biophys Acta* 1344: 201–209, 1997.