# Carnitine for the treatment of idiopathic asthenospermia: a randomized, double-blind, placebo-controlled trial

*Mark Sigman, M.D.,*[a] *Stacy Glass, R.N.,*[b] *Janice Campagnone, M.S.,*[a] *and Jon L. Pryor, M.D.*[b]

[a] Division of Urology, Brown University, Providence, Rhode Island; and [b] Department of Urology, University of Minnesota, Minneapolis, Minnesota

**Objective:** To determine the effect of oral carnitine supplementation on the semen parameters of men with idiopathic asthenospermia.
**Design:** Prospective, randomized, double-blind placebo-controlled study.
**Setting:** Academic tertiary referral centers.
**Patient(s):** Male patients presenting with infertility and with sperm motility of 10%–50% were selected.
**Intervention(s):** Patients were randomized to 24-week treatment arms of oral carnitine (2,000 mg L-carnitine and 1,000 mg L-acetyl-carnitine per day) or placebo.
**Main Outcome Measure(s):** Sperm motility and total motile sperm counts at baseline, 12 weeks, and 24 weeks. Seminal plasma and sperm free, acetyl, and total L-carnitine levels at baseline and at week 24.
**Result(s):** Twenty-one patients entered the study, with 12 patients in the carnitine arm and 9 in the placebo arm. There were no significant differences in baseline semen parameters between the carnitine and placebo arms. There was no statistically significant or clinically significant increase in motility or total motile sperm counts between baseline, 12 week, or 24 weeks in the carnitine or placebo arms.
**Conclusion(s):** Carnitine supplementation demonstrated no clinically or statistically significant effect on sperm motility or total motile sperm counts in men with idiopathic asthenospermia. (Fertil Steril® 2006;85: 1409–14. ©2006 by American Society for Reproductive Medicine.)

**Key Words:** Carnitine, male infertility, asthenospermia

The treatment of idiopathic male infertility remains problematic. Most proposed treatments, when subject to properly designed placebo-controlled randomized studies, have shown no efficacy. The majority of treatments have yet to be subject to these types of studies. Based on studies in other cell types, it has been suggested that acetyl-carnitine may serve several potential functions in sperm, such as transporting medium- and long-chain fatty acids into the mitochondria for metabolism, maintaining a proper acetyl-CoA:free CoA ratio by buffering excess acetyl-CoA, serving as a storage medium for acetyl groups which may then be used as an energy source, and serving as an antioxidant.

The highest levels of carnitine occur in the epididymis: epididymal concentrations of carnitine are approximately 2,000-fold higher than in the plasma (1). Low levels of seminal carnitine and acetyl-carnitine have been demonstrated in infertile men (2–4). In addition the acetyl-carnitine–L-carnitine ratio has been found to be reduced in semen from infertile men (5). Finally, uncontrolled studies have suggested an improvement in semen parameters of men with low sperm motility following treatment with oral carnitine (6–9). Taken together, these observations suggest a role of carnitine or acetyl carnitine as empiric therapy for idiopathic asthenospermia. The purpose of this study was to determine the effect of oral carnitine supplementation on the semen parameters of men with asthenospermia in a randomized, double-blind, placebo-controlled trial.

## MATERIALS AND METHODS

The study design consisted of a four-month period of treatment with either carnitine or placebo. No cross-over was performed, because the length of any residual effect and therefore the needed length of a washout period is unknown. The carnitine formulation consisted of 1,000 mg L-carnitine and 500 mg L-acetyl-carnitine (formulated as 1,552.5 mg L-carnitine fumarate and 227 mg microincapsulated L-carnitine

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Reprint requests: Mark Sigman, M.D., Division of Urology, Suite 174, 2 Dudley Street, Providence, Rhode Island 02905 (FAX: 401-444-6947; E-mail: mark_sigman@brown.edu).

fumarate, which is equivalent to 172.5 mg L-carnitine fumarate and 590 mg L-acetyl-carnitine hydrochloride). No antioxidants were present in the supplement. The formulation or a placebo was taken orally two times per day for a total daily dose of 2,000 mg L-carnitine and 1,000 mg acetyl-L-carnitine in the treatment arm. This dose is similar to that used in previously published uncontrolled studies.

Two semen samples were obtained at baseline, two months, and four months. In addition, baseline and four-month measurements were obtained for blood urea nitrogen (BUN), creatinine, liver function studies, blood lipids, glucose, urinalysis, complete blood count, FSH, and testosterone. Seminal plasma and spermatozoa free, acetyl, and total L-carnitine levels were determined at baseline and at four months by high-pressure liquid chromatography (10). The total carnitine measurement measured all forms of acyl-carnitine, therefore the sum of free and acetyl-carnitine may be less than the measured total amount when there are acyl-carnitines other than the acetyl form. Adverse events and patient compliance were noted.

Inclusion criteria included males aged 18 to 65 years with infertility of at least six months duration, sperm concentration of at least five million sperm/mL, motility of 10%–50%, absent pyospermia, and normal FSH and testosterone levels. Exclusion criteria included: a history of postpubertal mumps, cryptorchism, a history of vasal or epididymal surgery, a history of radiation therapy or chemotherapy, a recent history of alcohol abuse or chronic marijuana use, a history of current use of testosterone or any anabolic steroid, a history of exposure to significant environmental toxicants, or recent history of a fever, diabetes mellitus, liver failure, renal failure, any endocrine disorder affecting the hypothalamic-pituitary-gonadal axis, an untreated varicocele, acute epididymitis or orchitis, current genital tract infection, antisperm antibodies, obstruction of the genital tract, or a prior vasectomy reversal. Patients underwent a complete history and physical examination. Patients were randomized to receive carnitine or placebo. Both the investigators and the patient were blinded to the treatment arm assignment.

Semen samples were manually analyzed for volume, sperm density, motility, and forward progression. Motility and total motile sperm counts were the primary measures of efficacy and were analyzed by World Health Organization standard procedures (11). Although pregnancy was not a primary end point, any pregnancies that occurred during the study period were recorded. Statistical analysis was performed using Friedman test for repeated measures for non-parametric data (sperm density and total motile sperm counts) and Newman-Keuls multiple comparisons for parametric data (motility). Statistical significance was set at $P<.05$. Simple linear regression was used to evaluate the correlation between carnitine levels and motility. The study protocol was approved by the institutional review boards of both centers.

## RESULTS

Twenty-one patients completed the study, with 12 in the carnitine arm and 9 in the placebo arm. Five additional patients entered the study but dropped out before completion. One of these five dropped out because of pregnancy three months after starting carnitine. No patient dropped out because of adverse reactions. Mean patient age in the treatment group was 36.2 ± 1.7 years (standard error of the mean) which was not different than that of the treatment group (35.3 ± 2.5 years). Similarly the median total motile sperm count and percent motility of the treatment group were 29.4 million and 27.0% ± 2.4% respectively, which were not statistically different from the placebo group: 31.9 million sperm and 30.3% ± 3.2%. respectively ($P>.05$). All but one patient had been trying to conceive for over 12 months. One patient (age 52) requested evaluation after six months of attempted conception because of his age.

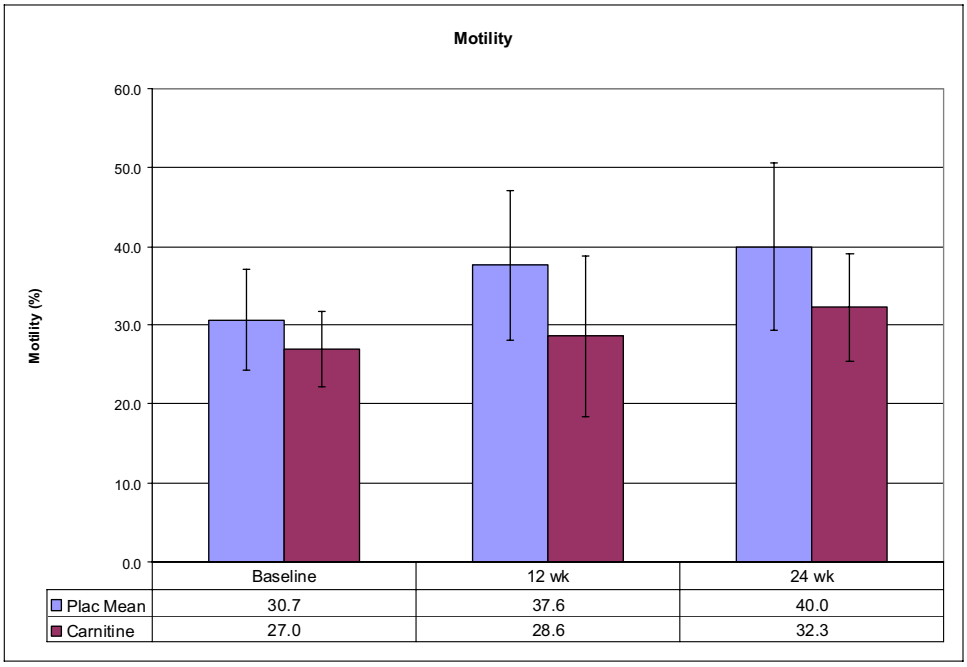
A trend toward an improvement in sperm motility was noted when comparing baseline with the 12-week and 24-week time points in both the placebo and the carnitine arm. These changes were not statistically significant (Fig. 1). In addition, the differences between motility in the carnitine and placebo arms at each of the three time points were not statistically significant. Similarly, there was a trend toward increasing total motile sperm counts when progressing from baseline to the 12-week and 24-week time points in both placebo and carnitine arms (Fig. 2). These changes were not statistically significant. In addition, differences in total motile sperm counts between carnitine and placebo were not statistically significant at any of the three time points. When examining individual patients, three patients in each arm had motilities at week 24 of at least ten percentage points greater than at baseline. One patient in the placebo arm and none in the carnitine arm had a motility decrease of greater than ten percentage points in the same time periods.

Baseline free, acetyl, and total L-carnitine levels were comparable between placebo and treatment arms (Tables 1 and 2). There were no increases in seminal plasma or spermatozoa free, acetyl, or total L-carnitine levels noted when comparing baseline to week 24 levels. In addition, levels were not statistically significantly different between placebo and treatment arms at either baseline or week 24 time points. There was no correlation between seminal plasma or spermatozoal free, acetyl, or total L-carnitine levels and sperm motility. Finally, there was no correlation between the change in seminal plasma or spermatozoa carnitine levels and change in motility (week 24 minus baseline) in the treatment arm.

Two pregnancies occurred: one in the treatment arm after IVF, and one in the placebo arm through intercourse. There were no changes in liver function studies (alanine aminotransferase, bilirubin), total cholesterol, serum creatinine, or BUN from baseline to the 24-week time point in either the placebo or the carnitine arm. There were no adverse events noted.

## FIGURE 1

Motility for placebo and carnitine arms at baseline, week 12, and week 24. Means ± standard error. Differences in motility between placebo and carnitine arms and between baseline and week 24 were not significant ($P>.05$).




*Sigman. Carnitine treatment for male infertility. Fertil Steril 2006.*

## DISCUSSION

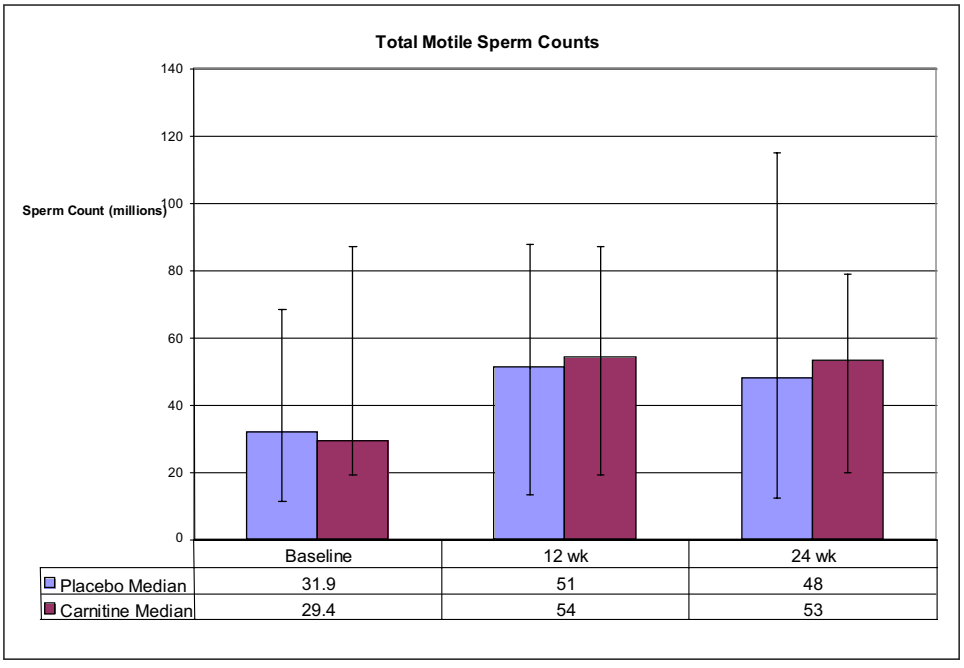
In humans, approximately 75% of the body's stores of L-carnitine are derived from the diet, whereas only 25% are synthesized de novo from lysine and methionine (12). L-Carnitine within the blood is taken up by epididymal tubule cells and then transported by active transport into the epididymal lumen. The concentration of free L-carnitine in serum is approximately 10–50 μmol/L (13), and in most tissues the concentration is 20- to 50-fold higher than in serum (14). In contrast, the concentration in the epididymal fluid is up to 2,000-fold higher than in serum (1). In the caput epididymal fluid or caput epididymal sperm, the concentration of free L-carnitine or acetyl L-carnitine is very low or undetectable. These concentrations increase dramatically during transit from the caput to the cauda epididymis.

Despite the known physiologic roles of carnitine in other eukaryotic cell types, the exact roles of carnitine in sperm remain, for the most part, unproven. Although carnitine plays an important role in the transport of fatty acids into the mitochondria for beta oxidation in eukaryotic cells, it is not clear that this process takes place in sperm or that medium-and long-chain fatty acids are an important source of energy for spermatozoa. In addition, short-chain fatty acids and acetate are transported across inner mitochondrial membranes in eukaryotic cells without the help of free carnitine. This is supported by the fact that the major acyl-carnitine present in spermatozoa, epididymal fluid, and seminal plasma is acetyl-carnitine and not medium- and long-chain fatty acyl-carnitines (15, 16). On the other hand, evidence does support a buffering role of acetyl-carnitine in maintaining sperm acetyl-CoA:CoA ratios. It is clear that high levels of acetyl-carnitine are present in sperm and seminal plasma, and although the use of the acetyl groups as an ongoing energy source seems likely it is unproven. Finally, the antioxidant role of carnitine, beyond buffering acetyl-CoA pools, has yet to be demonstrated in sperm.

A variety of clinical evidence also suggests a role for carnitine in sperm quality. Motility of poorly motile rat epididymal sperm was found to increase after the in vitro addition of L-carnitine and acetyl-carnitine (17). The addition of acetyl-carnitine and carnitine to ejaculated human sperm improves in vitro motility (18). In addition, a higher acetyl-carnitine:carnitine ratio was reported for sperm of higher motility than sperm of lower motility (the ratio of acetyl-carnitine to carnitine was 1.7 in extracts of sperm from samples with a low degree (0%–10%) of motility, whereas it was 4.7 in samples that were 40%–80% motile (16). Seminal plasma L-carnitine content has been correlated with sperm count and motility (4, 19). In addition, a reduction of acetyl-carnitine:carnitine ratio has been found in patients with poor sperm motility (5).

## FIGURE 2

Total motile sperm counts (millions of sperm) for placebo and carnitine arms at baseline, week 12, and week 24. Medians with 25% and 75% quartile ranges. Differences between placebo and carnitine arms and between baseline and week 24 were not significant ($P>.05$).




*Sigman. Carnitine treatment for male infertility. Fertil Steril 2006.*

Lower carnitine and acetyl-carnitine concentrations have been found in semen of infertile compared to fertile men (2). Clinical studies have reported an increase in sperm motility and sometimes sperm count in patients treated with oral carnitine (Table 3). In addition, improvements in motility have been reported in patients with a bacterial prostatovisiculoepididymitis and elevated seminal reactive oxygen species production, but only in those with normal seminal white blood cell concentrations (23). All of these studies have suffered from a lack of a placebo arm. In the present study there was a trend toward improved motility and total motile sperm counts in the placebo arm as well as the treatment arm. Although these changes did not reach statistical significance, they do point out that positive changes may occur and may not be due to a treatment effect.

The dose of 2,000 mg L-carnitine and 1,000 mg acetyl-L-carnitine is comparable to that used in other published studies. It is unknown if higher doses would have resulted in a different outcome. Lenzi et al. (21) have reported a double-blind placebo-controlled trial of carnitine therapy for males with oligoasthenospermia. In that study, a statistically significant improvement in sperm motility and sperm concentration was reported in the carnitine arm. However, that

## TABLE 1

**Seminal plasma carnitine levels at baseline and week 24.**

| | Baseline | | | Week 24 | | |
|---|---|---|---|---|---|---|
| **Arm** | **Free** | **Acetyl** | **Total** | **Free** | **Acetyl** | **Total** |
| Placebo | 449 ± 361 | 18.3 ± 21.7 | 642 ± 348 | 431 ± 162 | 41.4 ± 53.9 | 630 ± 186 |
| Carnitine | 508 ± 252 | 9.8 ± 4.5 | 594 ± 245 | 431 ± 179 | 17.8 ± 15.0 | 642 ± 224 |

*Note:* Units of measure are nmol/L (mean ± standard deviation). Differences in carnitine levels between placebo and carnitine arms and between baseline and week 24 were not significant ($P>.05$).

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**TABLE 2**

**Spermatozoal carnitine levels at baseline and week 24.**

| | Baseline | | | Week 24 | | |
|---|---|---|---|---|---|---|
| Arm | Free | Acetyl | Total | Free | Acetyl | Total |
| Placebo | 0.48 ± 0.49 | 0.21 ± 0.20 | 0.60 ± 0.42 | 0.46 ± 0.71 | 0.21 ± 0.20 | 0.75 ± 0.61 |
| Carnitine | 0.39 ± 0.29 | 0.16 ± 0.27 | 0.57 ± 0.43 | 0.46 ± 0.48 | 0.10 ± 0.10 | 0.64 ± 1.00 |

*Note:* Units of measure are nmol/million cells (mean ± standard deviation). Differences in carnitine levels between placebo and carnitine arms and between baseline and week 24 were not significant ($P>.05$).

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positive effect was noted only after the exclusion of five patients who were deemed outliers because of an excessive decrease of sperm motility during the washout period or an excessive increase of sperm motility during the second treatment period. With the exclusion of these five outliers, the absolute improvements in motility and sperm density, though statistically significant, were modest, motility increasing by 11% in the carnitine group compared to 8.8% in the placebo group and sperm density improving by 9 million sperm/mL in the carnitine group compared to 5.3 million sperm/mL in the placebo group. Because of the large sample size in that study, the differences were found to be statistically significant, although it is questionable if these minor differences are clinically significant. The present study is not powerful enough to have detected such small increases in motility or sperm density. However, the motility in the

**TABLE 3**

**Published carnitine trials for male infertility: effect on sperm count and motility.**

| | No. patients | Dose | Duration | Results |
|---|---|---|---|---|
| Nonrandomized noncontrolled studies | | | | |
| Moncada et al. 1992 (7) | 20 | 4 g acetyl L-carnitine/day | 2 months | Progressive motility up from 21.7% to 38.2% ($P<.003$) |
| Costa et al. 1994 (20) | 100 | 3 g L-carnitine/day | 4 months | Motility up 26.9% to 37.7%, progressive motility up from 10.8% to 18% ($P<.001$), total sperm count up from 142 to 163 million ($P<.001$) |
| Vitali et al. 1995 (9) | 47 | 3 g L-carnitine/day | 3 months | In 37/47 patients with impaired motility, motility up from 26.8% to 53.5% (3 patients stable SA; 7 patients worsened SA), no stats provided |
| Randomized controlled studies | | | | |
| Lenzi et al. 2003 (21) | 86 | 2 g L-cartinine/day | 2 months | Motility increased by 11% in carnitine group vs. 8.8% in placebo with 5 outliers excluded ($P=.02$) |
| Lenzi et al. 2004 (22) | 56 | 2 g L-carnitine + 1 g acetyl-L-carnitine/day | 6 months | No change in motility or sperm count ($P>.05$) |

*Note:* SA = semen analysis.

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placebo arm increased by 9.3 percentage points and the in the carnitine arm by only 5.3 percentage points. Thus a type II error is not likely a significant factor affecting the conclusions of the current study. Of particular note, eight pregnancies occurred during the L-carnitine therapy treatment period in the Lenzi study, whereas none occurred in the placebo therapy arm. In a recent second double-blind placebo-controlled trial of carnitine and acety-carnitine, Lenzi et al. found no statistically significant improvement in sperm concentration or motility (22).

One concern of oral carnitine therapy is the lack of a demonstrated improvement in seminal plasma or sperm carnitine or acetyl-carnitine levels following oral carnitine therapy. Lenzi et al. (21) also failed to demonstrate a change in seminal plasma levels in the carnitine arm. It is possible, but unproven, that changes in carnitine levels have not been noted because the baseline concentrations of these compounds are high to begin with, ruling out the possibility of detecting small but physiologically important increases in these levels. On the other hand, it is possible that the lack of improvement in semen parameters is because there is no increase in seminal plasma or sperm carnitine levels.

One finding that was very apparent during the conduct of this study was the great difficulty of recruiting American patients to participate in a placebo-controlled trial. At one of the sites, assisted reproductive techniques, including in vitro fertilization, were covered by insurance and many patients would rather proceed in that direction than take therapy that may potentially improve the male's fertility status but takes time. In addition, because carnitine is easily available, some couples elected to self-treat with carnitine rather than enter a study where they may have been given a placebo. These factors may account for the differences in the ease of recruitment of European versus American couples for these types of studies. Out of concern for rising health care costs and loss of time when pursuing ineffective therapies, these treatments should not be routinely employed unless part of a research protocol.

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