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Efficacy of L-Carnitine Therapy in Selected Cases of Male Factor Infertility

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Abstract

The purpose of the Placebo-controlled double-blind trial study is to investigate how effective the L-Carnitine therapy on cases of selected male factor infertility in a private clinic for 3 years duration. For this study, two hundred infertile male patients ages 20-40 years were chosen with the following basic sperm selection criteria: concentration, ≥20x10^6/mL, total motility, 10%-30%, forward motility, <70%, velocity, 10-30 micro/s, linearity, <4. <15%, atypical forms. Out of the selected sample, 172 patients completed the study. The patients were subject to L-Carnitine therapy of 1 g/day or placebo. The study course was as the following: 2 months of removing the L-Carnitine, 2 months of therapy/placebo, 2 months of L-Carnitine, and 2 months placebo/therapy. Different parameters were used to choose the male patients. The researcher selected sperm motility in specific. As a result, there was a statistically significant improvement in semen quality, better than the placebo alone. The improvement was noticed after the L-Carnitine therapy for sperm concentration and total and forward sperm motility. Those patients with lower values at the beginning of the study, i.e., <10x10^6 or <5x10^6 of forwarding motile sperm/ejaculate or sperm/mL manifested a more noticeable increase in forwarding sperm motility. In conclusion, L-Carnitine therapy proved to be effective in enhancing the semen quality, particularly among the patients with lower baseline levels. Yet, these results should be confirmed by larger clinical attempts in vitro studies.

Keywords: Fertility; Male Infertility; Oligospermia; Semen; Spermatozoa; L-Carnitine

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Introduction

There is a significant increase in infertility because of a possible decrease in semen quality [1]. 50% of the overall infertility is represented by the infertility factor of males, which represents a nowadays serious health and social problem in terms of both prevention and treatment [2]. Only when staying without children for a while though having unprotected intercourse that any man discovers that he suffers from infertility. There will be required diagnosis and treatment for the male when the man and the woman remain without pregnancy for a long time. Most of the time, even comprehensive clinical and laboratory checking might not help to diagnose the problem [2]. Several medicines identified as potential causes of male factor infertility associated with oligoastheno terato-zoospermia (OAT) of unknown origin. Therefore, to improve the quality of sperm, doctors including andrologists, endocrinologists, urologists, and gynecologists use medications whose efficiency is not ensured depending on symptoms narrated by the patient without a medical check. In a controlled attempt, there has been research on the efficacy of antioxidant medications on sperm maturation and the testicular-epididymal microenvironment [3]. The results were positive coming from a possible effect on epididymal spermatozoa [4]. It was obvious that the epididymis could be a possible target of treatment acting on spermatozoa in cases of idiopathic OAT. The physiological role of the epididymis is to be active in spermatozoa metabolism through the many compounds secreted or produced by the epithelium; among these, Carnitines are gathered as both free and acetylated L-Carnitine and are used by spermatozoa for mitochondrial beta-oxidation of long-chain fatty acids, this being the principal shuttle and transfer system of the acyl to the mitochondrial CoA [5,6]. Besides, Carnitine functions on the cell DNA and membranes to protect them against damage caused by free oxygen radicals [7]. Moreover, early in the 1990s, an experimental uncontrolled study by many centers testing the efficacy of L-Carnitine in selected cases of OAT yielded in several positive results on sperm motility [8]. Another recent controlled study on the use of L-Carnitine and L-acetyL-Carnitine in patients with male genital tract inflammation manifested that Carnitines are an effective treatment in patients with a bacterial prostato-vesiculo-epididymitis and increased free oxygen production, even when seminal v, white blood cell concentration is normal [9].

Methods

Study Design

Patients undergone a therapy of L-Carnitine (1 g/day orally) or an equal volume of seemingly identical placebo. The L-Carnitine dose was

the same dose that was used in previous experiments on this matter [8]. The study design was 2 months of no drug, 2 months of therapy/placebo, 2 more months of no drug, 2 more months of placebo/therapy, and 2 months of follow-up (controls at months T-2, T-1, T_0, T+2, T+4, T+6, and T+8). There was a monthly evaluation of three semen samples before the beginning of therapy (T-2, T-1, and T_0) to test semen stability in each patient as stated by WHO [10].

For each control, complete microscopic semen analysis was conducted to evaluate semen and sperm parameter modifications. For this study, the effective criterion was the improvement in sperm variables, and, among such parameters, improvement in sperm motility (both total and forward) was the main measurement of success. This enhancement was due to both the expected effect of L-Carnitine on sperm metabolism and the results of previous trials, which were proved by recent findings [8,9].

Semen Analysis

Semen analyses using the microscope were implemented by the same biologists using WHO [10] standard procedures and our own standards. The researchers gathered the samples through masturbation after a 3- to 5-day period of sexual abstinence. The semen variables taken into consideration were volume (mL) and pH of ejaculate, sperm concentration ($n\times10^6$/mL), total sperm number (n×volume of ejaculate), total and forward sperm motility (percent 1 hour after ejaculation), sperm velocity (mm/s), and linearity (index).

Total motile spermatozoa/mL and spermatozoa/ejaculate and total forward motile spermatozoa/mL and spermatozoal ejaculate were also calculated by multiplying the percent of total or forward sperm motility, respectively, by sperm concentration/mL and total sperm number per ejaculate.

Study Group and Eligibility

The study group of 200 patients was chosen from more than 1,000 individuals visiting our private clinic (from the beginning of 2010 to the end of 2012) for their first consultation relating to male factor infertility. The general inclusion criteria for selection were age between 20 and 40 years, infertility for longer than 1 year, and regular sexual intercourse with a gynecologically normal partner without obvious factors of female factor infertility (biphasic basal body temperature, evaluation in luteal phase, ultrasound ovary and uterus evaluation, and histerosalpingogram to study tubal patency). As for the specific inclusion criteria, they included absence of general and endocrinological diseases (studied by clinical examination and routine and hormonal laboratory tests), present or previous cryptorchidism, genital infections or genital tract obstructions, varicocele and testicular hypotrophy or antisperm antibodies [11]. To avoid potential impacts of variable L-Carnitine consumption in food, patients were requested to follow a standard diet. None of them suffered from any deficiency in L-Carnitine metabolism. The seminological inclusion criteria were normal rheological characteristics (appearance, consistency, and liquefaction), volume and pH in the normal range, sperm concentration $\geq20\times10^6$/mL, total motility 10%-30%, forward motility <15%, atypical forms <70%, semen leukocytes $<1\times10^6$/mL, and sperm velocity and linearity of 10-30 m/s and <4, respectively. These upper and lower limits permit the inclusion of cases of mild oligoasthenospermia and were selected based on possible L-Carnitine action on sperm energetic metabolism and on protection against oxidative damage. The lower limits permitted the exclusion of cases of very severe OAT linked to irreversible primary or secondary testicular damage, which would prevent observance of positive or negative effects on seminal variables, as this was, to our knowledge, the first placebo-controlled study of Carnitine use in OAT treatment. To be included in the trial, patients had to meet the above seminological inclusion criteria at the time of the first control (T-2), maintain sperm variables within this range for the further two washout controls (T-1 and T_0), and show no statistically significant differences in the three evaluations before treatment (T-2, T-1, T_0).

Statistical Analysis

Means and SD were calculated on all clinical and seminal variables at each time control. Then variance for repeated measures was analyzed on the initial three washout semen analyses to test differences between these controls. The primary and secondary efficacy analyses were done on the difference between the end point and baseline values of each test period. The difference value was calculated through the differences in sperm variables for each test period (i.e., [variable at (T+2) -"variable at T_0] and [variable at (T+6) -variable at (T+4)], respectively). This was performed on both raw data (e.g., j motility percentages) and absolute values in terms of millions of spermatozoa/mL and spermatozoa/ejaculate, which were obtained by multiplying the sperm concentration/mL and spermatozoa/ejaculate by the percent of the total and forward sperm motility. The latter values were used for the diagrams. To exclude transient decrease in semen quality during washout periods followed by a too sudden improvement, independent of treatment, in the following observation periods, we evaluated the existence of similar outlier situations. Only five patients exhibited these situations and in the period from T-2 to T+2. We added the following exclusion criteria: further evaluations were implemented after exclusion from the statistical analysis of those patients with both a high decrease from T-2 and T_0 (from 30% to 10%) and a response in terms of improvement of sperm motility from T_0 to T+2 greater than 30%. Subgroups with more critical values of forward motile sperm per ejaculate and per milliliter (<10 and $<5\times10^6$, respectively) were also subjected to efficacy analyses with regard to differences of absolute number of motile spermatozoa.

Results

Out of the 200 patients included, 170 completed the study. Eleven pregnancies were achieved during the observation period. Evaluation of female partner menstrual history showed that all pregnancies were achieved during the L-Carnitine therapy period (six during the first period of therapy with L-Carnitine and five during the second in patient's first passing through treatment with placebo). Out of the 30 patients not completing the study, six decided to undergo assisted reproduction (three during therapy and three during placebo treatment), 18 patients did not come back for the second period of treatment (eight after a period of therapy and ten after placebo treatment). Six of 11 patients inducing pregnancy during the study decided to stop treatment (all after a therapy period). Table 1 show values for semen volume, sperm concentration, motility, and morphology over the pretreatment period. The three semen analyses conducted before treatment did not yield statistically significant differences in the analysis of variance for repeated measures conducted overall patient population (3×200 analyses). Therefore, values calculated at the beginning of the first treatment (T_0) were acceptable as the baseline for further comparisons. The patient groups showed no differences at T_0 between therapy or placebo cycle in semen parameters. Moreover, the sequence of treatment was not significant for sperm variables. Specifically, the analysis for total and forward motility gave results of P = 461 and 0.526, respectively.

Table 1: Analysis of variance for repeated measures on the three washout semen measures of all selected patients Means ± SD and *P* values).

	T-2	T-1	T_0	P
Semen Volume(ml)	3.28±1.56	3.21±1.50	3.25±1.58	0.945
Sperm Concentration (n x10^6 ml)	15.88±3.17	16.04±4.19	16.17±4.66	0.890
Total Motility (%)	25.35±5.51	24.14±5.0	25.51±5.18	0.128
Forward Motility (%)	12.53±3.30	11.67±3.50	12.58±3.74	0.126
Atypical Forms (%)	68.57±2.97	68.06±3.07	68.17±2.68	0.441

Table 2: Variation in sperm concentration (n×10^6) in total and forward sperm motility (%) and linearity (index) during treatments (placebo/therapy or vice versa) by excluding outlier data of five patients (Δ and *P* value of 370 therapy/placebo cycles).

	Period 1 (from T_0 to $T+_2$)					Period 2 (from T_4 to T_6)		
	Δ[(T+2)-T_0]	Δ[(T+2)-T_0]	Δ[(T+2)-T_0]	Δ[(T+2)-T_0]	Δ[(T+2)-T_0]	Δ[(T+6)-(T+4)]	Δ[(T+6)-(T+4)]	Δ[(T+6)-(T+4)]
Treatment	Total Sperm Motility	Forward Sperm Motility	Sperm Concentration	Sperm Linearity	Total Sperm Motility	Forward Motility	Sperm Concentration	Sperm Linearity
L-Carnitine	11.0^a	16.4^b	9.0^c	0.6^d	3.4^a	4.5^b	3.7^c	0.2^d
Placebo	8.8^a	13.9^b	5.3^c	0.4^d	-0.1^a	0.7^b	-0.7^c	-0.2^d

Where: ap = 0.04; bp = 0.05; cp = 0.01; and dp = 0.03

Both sequences were used in the analysis that followed. And because each patient received treatment with the therapy and placebo, we ended up with 370 cycles of treatment periods for comparison.

Five patients at T_0 demonstrated the lower borderline total motility value (i.e., 10%), with a decrease during the washout period (from 30% at T-2 to 10% at T_0) and showed a great difference (i.e., >30%) between the control T_0 and T+2. These differences in sperm motility are separate from the treatment: three of these patients received placebo and two received L-Carnitine in the first period. The first and second treatment periods of these patients did not go through extra analyses. Therefore, twenty (20) therapy/placebo cycles were excluded, so the total number of therapy/placebo cycles used in the analysis was 350.

During the treatment with placebo, there was noticed an improvement in Semen quality. Statistical efficacy analysis comparing the differences of sperm values after and before L-Carnitine treatment and after and before placebo treatment permitted not only exclusion of baseline value interference, but also noticing the real differences between therapy and placebo outcomes.

There was no significant statistical difference analysis (**Δ**) between the raw data of percent of total and forward sperm motility, and on the first period alone of all 350 therapy/placebo cycles, although the improvement in total and forward sperm motility was higher in the therapy than in the placebo period.

However, statistically significant differences were observed in total and forward motility percentages (P = 0.04 and P = 0.05, respectively) using the same analysis when the five borderline and outlier patients were excluded from the statistical analysis (Table 2). Similarly, statistically significant positive results of a major increase during L-Carnitine therapy compared with placebo were observed for sperm concentration (P = 0.01) and sperm linearity (P = 0.03) by excluding the above reported five patients (Table 2).

Figures 1 and 2 illustrate the increase in total motile spermatozoa/mL and forward motile spermatozoa/mL gained through using absolute values proved in millions of motile spermatozoa present in the ejaculate and their **Δ**-values.

Thus avoiding potential interferences is due to spontaneous differences in semen volume. The p value on these variations was again highly significant (P = 0.008 and 0.006, respectively).

The increase assessed by variations of forward motile spermatozoa during the therapy period was significantly higher in the most critical patients, i.e., in those patients with an initial value of <10×10^6/mL forward motile sperm/ejaculate and above all in those with <5×10^6/mL forward motile sperm/ml.

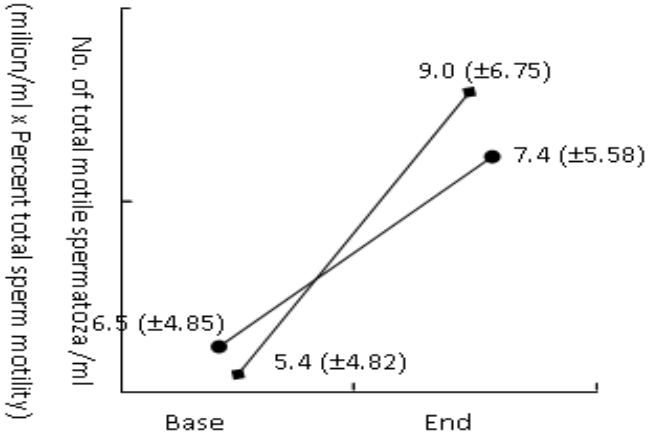

Figure 1: Diagram of difference (Δ) in absolute values expressed in millions of total motile sperm/mL from the beginning (base) to the end of the L-Carnitine therapy (line with diamonds) and placebo (line with circles) cycles. Values are Means ± SD (P = 0.008).

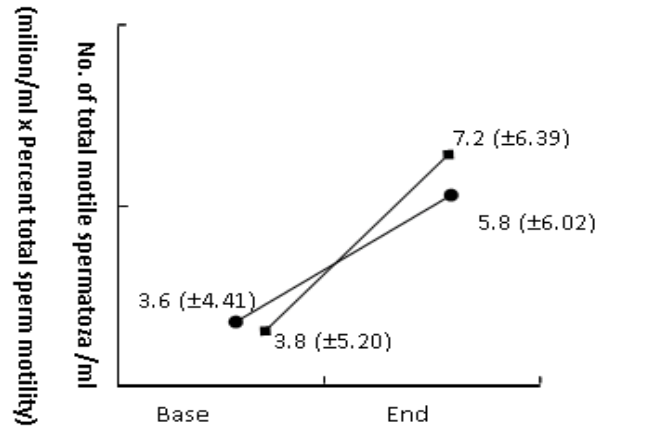

Figure 2: Diagram of difference in absolute values expressed in millions of forward motile sperm/mL from the beginning (base) to the end of the L-Carnitine therapy (line with diamonds) and placebo (line with circles) cycles. Values are Mean ± SD (P = 0.006).

Table 3: Variation in forward motile spermatozoa during treatments (placebo/therapy or vice versa) for patients with 10×10^6/mL forward motile sperm/ejaculate (Means ± SD of the absolute number of forward motile spermatozoa in millions, Δ and *P* values) (P = 0.03).

	Period 1 (from T_0 to T+2)			Period 2 (from T_4 to T_6)		
Treatment	**T_0**	**T+2**	**Δ**	**T+4**	**T+6**	**Δ**
L-Carnitine	2.9±1.2	14.1±11.0	11.2	2.0±1.7	17.4±28.0	15.4
Placebo	3.3±1.1	10.2±7.3	6.9	2.3±1.4	6.2±7.8	3.9

Table 4: Variation in forward motile spermatozoa during treatments (placebo/therapy or vice versa) for patients with $<5\times10^6$/mL forward motile sperm/mL (Means ± SD of the absolute number of forward motile spermatozoa in millions, differences and *p* values (P = 0.02).

	Period 1 (from T_0 to T+2)			Period 2 (from T_4 to T_6)		
Treatment	**T0**	**T+2**	**Δ**	**T+4**	**T+6**	**Δ**
L-Carnitine	1.5±0.4	6.2±3.9	4.7	1.0±0.6	5.5±8.2	4.5
Placebo	1.4±0.4	5.0±4.0	3.6	1.0±0.7	2.4±2.8	1.4

As shown in Tables 3 and 4, in these subgroups, there was a noticeable variation between the L-Carnitine therapy and placebo periods in the absolute number of forward motile spermatozoa in millions (P = 0.03 and P = 0.02, respectively). The number of patients improved during therapy with the number of those improving during the placebo cycle yielded results of P = 0.04 and 0.004, respectively, for patients with $<10\times10^6$ and forward motile sperm/ejaculate and $<5\times10^6$ forward motile sperm/mL.

Discussion

Recently, numerous ways of assisted reproduction have been presented as a potential solution for "male factor" infertility. These methods, rather than being a deathblow for andrology, have been a main cause for research into sperm function. However, they have also halted the development of new strategies for male factor infertility therapy. Controlled studies in this field have common problems and options with all clinical attempts but also have some special difficulties: case selection criteria, patient acceptance of the placebo period, variables to be analyzed, sperm parameters (having spontaneous variability), sperm function tests (not yet sufficiently standardized), spontaneous pregnancy rate (subject to female contribution).

Sadly, as a result, many medicines are used to treat male factor infertility without any rationale: such therapies are often prescribed sequentially without any positive effect, and any depicted enhancements in semen parameters are without a real basis and could be the result of natural fluctuations in semen quality. Some of these therapies were also proposed before in the international ' literature and were criticized very much [12]. The claimed purpose is to amplify spermatogenesis, increase the highest quality sperm populations, and act on the sperm maturation and energetic metabolism and on the testicular-epididymal microenvironment. Among these proposed actions, postgonad maturation could be a potentially rational and interesting target especially as it occurs mainly in the epididymal fluid where spermatozoa are away from the complex but only partially understood intratesticular hormonal network. In the epididymis, the epithelium eliminates some testicular factors, absorbs material from the blood, and produces specific compounds, all useful for sperm maturation and motility. Among these, in the mammalian epididymis, the free L-Carnitine is taken up from the blood plasma, moved into the epididymal fluid and into the spermatozoa, and gathered as both free and acetylated L-Carnitine. This small, quaternary amine-free L-Carnitine is one of the most concentrated water-soluble polar substances present at the epididymal level (hundreds of times more concentrated than in blood).

Free L-Carnitine (3-hydroxy-4-N-trimethylaminobutyric acid) was first taken from bovine muscle in 1905, and its structure was definitively established in 1927 [5]. Its main feature is the biological importance in mitochondrial beta-oxidation of long-chain fatty acids, as proven by Fritz in 1963. Before entering the mitochondria, fatty acids must be activated, i.e., they must bind to the CoA to form acyl-CoA. Long-chain molecules of acyl-CoA cannot get across the internal mitochondrial membrane. Thus, they need a specific enzymatic transporting system. After the transport of the acyl into the mitochondria, acyl Carnitine transfers the acyl to the mitochondrial CoA and exits as free Carnitine to start a new transport cycle [5]. Carnitine also acts in the cell membrane as an "anti-aging" substance, protecting against damage induced by free i oxygen radicals. It prevents protein oxidation and pyruvate ' and lactate oxidative damage. In humans, 75% of Carnitine comes from diet as other water-soluble substances, while 25% is synthesized from lysine and methionine, although the enzyme that catalyzes the hydroxylation of the 4-butirrobetain in L-Carnitine, 4-butirrobetain hydroxylase, is present in few tissues [6].

Based on what we learned so far about the action of Carnitine on cellular metabolism, and from outcomes gained in a previous (uncontrolled) multicenter study [8], and recently confirmed in selected andrological pathologies [9], we selected L-Carnitine as possibly active on parameters relating to male factor infertility and conducted the present controlled study (double blind vs. placebo, crossover). We used a 2-month therapy/placebo period to concentrate on the effect directly facilitated by Carnitines on spermatozoa or late spermatogenesis phases. Considering the selection criteria of a number of patients, and the number of seminal analyses performed for each patient in a controlled trial, the results obtained and all the well-known difficulties involved in performing such rigorous studies and interpreting their results were yielded accordingly.

We attempted to minimize potential bias in the general scheme of the study. The washout period with three semen analyses before the start of therapy allowed evaluation of the therapeutic effect while reducing the possible effect of spontaneous variations in seminal characteristics [10].

The 2 month washout period between administration of the therapy and placebo (or vice versa) avoided incorrect attribution of their effects.

We noticed that there were improvements in the variables analyzed even during administration of the placebo that could be only partial due to the statistical phenomenon of regression to the mean. Further, the therapy showed a stronger positive effect in the first period of administration than in the second. The outcomes indicate with confirmation that psychological factors play an important role even in infertility, as a result to the feeling of being treated.

The most expected effect from a prognostic point of view of the

patient's fertility was that on impaired sperm motility. The reason for this effect must be the metabolic energetic action of L-Carnitine and its activity as an anti-oxidant compound [13]. Using the sperm motility/mL and sperm motility/ejaculate percentage data of all patients, the difference in improvement between therapy and placebo, although present, was not statistically significant.

The improvement becomes statistically significant when the outlier data of those patients who showed a spontaneous decrease in sperm motility during the washout period were eliminated. This reduction was too great to exclude a transient, although asymptomatic, pathology followed by a too sudden and large improvement in the first treatment period that appears independent of that same treatment. Moreover, when using absolute data of total number of spermatozoa with motility or forward motility present in the ejaculate, the outcomes become highly statistically significant. This last analysis allows exclusion of the confounding effect of semen volume variation, which is not dependent on the therapy. The significant increase in sperm linearity and the no significant variation in sperm velocity signal a selective effect on the qualitative mechanisms of sperm kinetics. The effect on sperm motility is more interesting by the fact that its greatest effect is found in the most critical cases, that is, those with the lowest initial forward motile sperm concentration. The effects on these subgroups were very interesting from both a speculative and clinical point of view. First, we can hypothesize that even with a reduced spermatogenesis, biochemical deficiency in the energetic metabolism of mitochondria in such patients could be corrected by a high dose of intracellular Carnitine. Second, these results, showing a possible action of L-Carnitine even in cases of very severe OAT (e.g., sperm motility <10%). While the effect on sperm motility was suggested by the metabolic action of the Carnitine, the effect noticed on sperm concentration was unexpected. The characteristics of Carnitine would not lead one to expect a direct effect on the first phases of spermatogenesis, but rather on post-testicular sperm maturation, it was impossible to spot an effect on the complete spermatogenic cycle. This effect on sperm concentration may be due to an unknown effect in Sertoli cell-spermatogenic line interaction, to an action on the postmeiotic phases of spermatogenesis (for example, on the chromatin stability or mitochondrial function of spermatocytes or spermatids). The effect could also be attributed to an improvement in homeostasis and the quality of the epididymal microenvironment, reducing gamete phagocytosis at this level while increasing ejaculated spermatozoa.

The lack of effects on sperm morphology, considered as one of the most sensitive indices of the efficacy of spermatogenesis, seems to confirm the hypothesis of a post-testicular effect. At the end, even though pregnancy is not the principal end for this controlled study because of the many possible interferences, the eleven pregnancies, with spontaneous in vivo fertilization all obtained during the L-Carnitine therapy period, from a group of patients with long-term infertility could suggest that Carnitines may also lead to an improvement in sperm function and fertilization capacity. This could be a further indication for future studies including patients undergoing assisted reproduction. To confirm all the above, it will also be necessary to study in vitro the effect of Carnitine on the metabolism of the male gamete with molecular and cellular studies and to carry out longer and multicenter controlled trials.

Conclusion

A general recommendation is that both clinical reproduction specialists and general practitioners should receive andrological training to be able to diagnose and treat pathologies associated with a decrease in male fertility, e.g., cryptorchidism, varicocele, sexually transmitted diseases, environmental and work factors, and lifestyle. When andrological pathologies are not evident, only those therapies that have been subjected to controlled studies should be used to treat OAT. L-Carnitine therapy, submitted to such a study, showed some interesting positive effects in increasing semen parameters that merit further investigation.

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