

## Effect of L-carnitine, Multivitamins and their Combination in the Treatment of Idiopathic Male Infertility<sup>#</sup>

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### Abstract

The aim of the present study is to investigate and compare the efficacy of L-carnitine, multivitamins and their combination therapies on semen characteristics in idiopathic male infertility. Idiopathic infertile patients were randomly divided into three groups who had received three different treatment regimens for three months: group A (45 patients) has received 2 grams daily of L-carnitine alone; group B (55 patients) had received the combination of L-carnitine (2 grams daily) plus one tablet daily of multivitamins (Stresstabs®); and group C (29 patients) had received one tablet daily of multivitamins alone. The study was started on 1/11/2009 and completed on 31/3/2010 and performed at Rizgari Teaching Hospital in Hawler City/Erbil Governorate. Thirty fertile male volunteers were used as a control group as well. Seminal fluid analysis has been done before treatment and then monthly after treatment for three month. The results of the present study clearly demonstrated that the combination therapy of L – carnitine and multivitamins was more efficient than each drug therapy alone and this evidenced by improvement and significant increase in the semen parameters; sperm concentration (72%), sperm count (79%), actively motile sperm (29%), and progressive motile sperm count (125%) when compared to pretreatment values than either L – carnitine or multivitamins therapy alone (53%, 60%, 19% and 84%), (21%, 30%, Non Significant, 34%) respectively. The results demonstrated that the combination therapy of L-carnitine and multivitamins was more efficient and produced more significant improvement in semen characteristic than either therapy alone, and that L-carnitine therapy was more efficient than multivitamins. Improvement in these semen parameters can aid in the treatment of idiopathic male infertility.

**Key words :** L-carnitine, multivitamins, infertility.

**تقييم ل - كارنتين والفيتامينات المتعددة وكلاهما سوية لعلاج مرض عقم الذكور مجهول السبب**  
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### الخلاصة

إن هدف هذه الدراسة هو التحقق عن ومقارنة كفاءة علاجات ل - كارنتين أو الفيتامينات المتعددة أو كلاهما معا على خصائص السائل المنوي (حجم السائل المنوي، تركيز الحيامن، عدد الحيامن، شكل الحيامن، حركة الحيامن، عدد الحيامن ذات الحركة المتقدمة، وعدد الخلايا المدورة). في عقم الذكور مجهول السبب في محافظة اربيل، هادفة إلى تحسين هذه الخصائص خلال ثلاثة أشهر من العلاج ولاكتشاف الطريقة الصحيحة لتقديم البيانات المخبرية لتحليل السائل المنوي والتي يتم عملها في محافظة اربيل. في هذه الدراسة تم تقسيم ١٢٩ مريض ( والعقم مجهول السبب ) بطريقة عشوائية إلى ثلاثة مجاميع كل منها اخذ علاج يختلف عن الآخر لمدة ثلاثة أشهر مستمرة:

المجموعة - أ - (٤٥ مريض) تناولوا ٢ غرام من ل - كارنتين يوميا،

المجموعة - ب - (٥٥ مريض) تناولوا ٢ غرام من ل - كارنتين مع حبة واحدة من الفيتامينات المتعددة (ستريستابز®).

المجموعة - ج - (٢٩ مريض) تناولوا حبة واحدة من الفيتامينات المتعددة (ستريستابز®).

وقد تم اخذ وتسجيل مجموعة أخرى (الكونترول) في هذه الدراسة والتي تضمنت ٣٠ متطوع ذكر خصب. لقد تمت متابعة المرضى وتم تحليل السائل المنوي قبل البدء بأخذ العلاجات وشهريا خلال اخذ العلاج لمدة ثلاثة أشهر. هذا وقد تم استخدام فحص (t) ذو النموذج الزوجي للمقارنة بين القيم قبل العلاج والقيم المقابلة لها بعد شهر وشهرين وثلاثة أشهر من العلاج، وقد اعتبرت قيمة احتمالية الصدفة (P) ذات أهمية إحصائية عندما تكون قيمتها اقل من ٠,٠٥. لقد أظهرت نتائج هذا البحث بصورة واضحة إن ل - كارنتين المستخدم بجرعة ٢ غرام يوميا لمدة ثلاثة أشهر مستمرة ممكن أن يحسن تركيز الحيامن، عدد الحيامن، نسبة الحيامن المتحركة بصورة فعالة، وعدد الحيامن ذات الحركة المتقدمة عند الرجال الذين يعانون من العقم (قلة تركيز الحيامن او قلة سرعتها او كلاهما) مجهول السبب، وإن العلاج الذي يجمع بين ل - كارنتين و الفيتامينات المتعددة لمدة العلاج نفسها هو اكثر كفاءة ( حصول زيادة مهمة احصائياً في خصائص السائل المنوي المذكورة أعلاه بمقدار ٧٢%، ٧٩%، ٢٩%، ١٢٥% بالتعاقب مقارنة مع القيم المقابلة لها قبل العلاج ) من علاج ل - كارنتين لوحده ( حصول زيادة مهمة احصائياً في خصائص السائل المنوي المذكورة اعلاه بمقدار ٢١%، ٣٠%، غير مهم احصائياً، ٣٤% بالتعاقب مقارنة مع القيم المقابلة لها قبل العلاج ) لتحسين خصائص السائل المنوي هذه ومن الممكن أن يساعد في علاج عقم الرجال مجهول السبب. بالإضافة لذلك، علاج ل - كارنتين من الممكن أن يكون أفضل من علاج مجموعة الفيتامينات المتعددة باستخدام نظام العلاج الذي تم تطبيقه في هذه الدراسة في تحسين خصائص السائل المنوي علاج عقم الرجال مجهول السبب.

**الكلمات المفتاحية :** ل - كارنتين ، فيتامينات ، عقم .

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## Introduction

Male infertility means the male is unable to impregnate the female because of male factors. It represents 25-40% of the total causes of infertility<sup>(1)</sup>. Although the etiology of male infertility is not clear in most cases, different treatment options have been suggested to increase sperm count and motility<sup>(2)</sup>. These treatment options include general, medical and surgical management. Medical treatment includes gonadotrophins, androgens, corticosteroids, antibiotics, alpha-sympathomimetics, anticholinergics, antiestrogens, aromatase inhibitors, and alternative therapy which is considered the safest among the treatment options and include antioxidants (multivitamins) and L-carnitine<sup>(3)</sup>. Carnitine is a zwitterionic amino acid (3-Hydroxy-4-trimethylamino-butyric acid). It is found in different food items and derived endogenously from lysine and methionine<sup>(2)</sup>. L-carnitine is an essential cofactor that could accelerate lipid metabolism and has a pivotal role in mitochondrial  $\beta$ -oxidation of long-chain fatty acids for cellular energy production<sup>(4,5)</sup>. L-carnitine and L-acetylcarnitine are highly concentrated in the epididymis and play a crucial role in sperm metabolism and maturation<sup>(6)</sup>. The redox system in the spermatozoa regulates the processes that are crucial for fertilization<sup>(7)</sup>, but increased reactive oxygen species (ROS) observed in semen of infertile men might cause cellular damage and this have brought about the widespread use of antioxidants<sup>(8)</sup>. Many vitamins such as vitamin C, vitamin E, vitamin B<sub>12</sub>, and many other antioxidants were used to improve sperm quality for the treatment of idiopathic oligoasthenozoospermia<sup>(9)</sup>. In addition, sperm concentration was increased in a number of studies on subfertile men after treatment with zinc and folic acid<sup>(10, 11)</sup>. The aim of the present study is to investigate and compare the efficacy of L-carnitine, multivitamins and their combination therapies on semen characteristics (seminal fluid volume, sperm concentration, sperm count, sperm morphology, sperm motility, progressive motile sperm count and round cells count) in idiopathic male infertility.

## Patients and Methods

**Settings:** This randomized interventional study has been accomplished cooperatively with the laboratory of the Department of Pharmacology in the College of Pharmacy/ Hawler Medical University (Hawler Medical University is beside Rizgari Teaching Hospital), the Laboratory of Rizgari Teaching Hospital, Dr. Hunar Abdul Qadir's Clinic, and Shai and

Luay Laboratories in Hawler city / Erbil Governorate/ Iraqi Kurdistan Region. The practical work of this research has been started on 1/11/2009 and completed on 31/3/2010. The research was authorized and approved by the Board and Ethical Committee of Hawler Medical University, Erbil, Iraq.

## Subjects and Patients

**Control group:** included 30 fertile male volunteers diagnosed by the urologist, their ages ranged between 21 to 38 years; the results of their seminal fluid analyses were within the normal values and this test was done and recorded for them one time only.

**Patients' inclusion criteria :** were infertile or subfertile young males diagnosed by the urologist with age range between 20 to 42 years, absence of leukocytospermia in the semen samples taken before the start of the treatment period, and absence of endocrinopathies or known etiology or female infertility factors.

**Protocol:** all 129 patients had received their treatments for 3 months. Group A (45 patients) had received 2 grams per day of L-carnitine (Nature's Bounty, INC./USA) in 4 divided doses. Group B (55 patients) had received 2 grams per day of L-carnitine in 4 divided doses plus 1 tablet daily of multivitamins with zinc (Stresstabs® Weyth healthcare/ Canada). Group C (29 patients) had received 1 tablet of Stresstabs® daily. Seminal fluid analysis was done and recorded for each patient before treatment and monthly during the treatment.

## Collection of seminal fluid:

Samples were collected following a period of sexual abstinence from 2 to 3 days to no longer than 7 days. Most of the patients had collected their semen samples in the laboratory and analysis was performed within 30 minutes by the same examiner. Average readings were taken. Questionnaire paper contained the following questions were prepared and answered by the patients and the controls.

1. The name of the patient.
2. The age of the patient and his wife.
3. Mobile number.
4. Years of Marriage.
5. Years of infertility.
6. Number of children.
7. Smoker or alcoholic.
8. Past and recent medical history.
9. Past and recent surgical history.
10. Past and present illnesses.

11. Weight of the patient (if obese then look for the cause).
12. The type of the diet.
13. The occupation of the patient.
14. Exposure to toxins like lead, mercury, pesticides, or radiation.
15. Presence of female infertility factors.
16. The date of starting the interventional treatment.
17. The assigned dates of the sperm analysis during the treatment.
18. The assigned date of ending the interventional treatment.

**Laboratory procedures:** seminal fluid analysis done (according to Strasinger and DiLorenzo, 2008<sup>(12)</sup>, WHO 2010<sup>(13)</sup>) had included the following: recording the semen color, odor, viscosity, liquefaction, and pH of seminal specimen; measurement of seminal fluid volume, sperm count and concentration, sperm morphology, sperm motility (percentage of active, sluggish, immotile sperms, and

progressive motile sperm count, (sperm count x percent active motile count), and round cell count.

**Statistical analysis:** All the seminal fluid and sperm parameters in all of the groups were represented as the mean  $\pm$  the standard error (SE). Paired sample t-test was applied to compare between the values before treatment and their corresponding values after 1, 2, and 3 months of treatment. P values of  $< 0.05$  were considered statistically significant. \* $p < 0.05$  represents significant difference between before treatment and after treatment. Different letters represent significant difference between controls and the patients before treatment.

## Results

Twenty idiopathic infertile patients were dropped out during the treatment before we had reached to the above final numbers of participated patients.

### Group A patients

**Table 1: Effects of L-carnitine treatment on the mean  $\pm$  SE of seminal fluid volume, sperm concentration, and sperm count in idiopathic infertile patients (n=45) compared to controls (n=30).**

Patients/Controls	Seminal Fluid Volume (MI)	Sperm Concentration (Million/MI)	Sperm Count (Million/Ejaculate)
Controls	2.63 $\pm$ 0.13	63.26 $\pm$ 10.08 a	168.96 $\pm$ 31.82 a
Patients before treatment	2.63 $\pm$ 0.20	20.08 $\pm$ 1.59 b	51.42 $\pm$ 5.41 b
1 Month after treatment	2.67 $\pm$ 0.15	24.82 $\pm$ 2.42 *	67.23 $\pm$ 7.21 *
2 Month after treatment	2.66 $\pm$ 0.14	28.82 $\pm$ 3.23 *	74.16 $\pm$ 8.37 *
3 Month after treatment	2.74 $\pm$ 0.17	30.88 $\pm$ 2.63 *	82.41 $\pm$ 8.78 *

\* $p < 0.05$  represents significant difference between before treatment and after treatment. Different letters represent significant difference between controls and the patients before treatment.

**Table 2: Effects of L-carnitine treatment on the mean  $\pm$  SE of sperm motility (represented as percent of total) in idiopathic infertile patients (n=45) compared to controls (n=30).**

Patients/Controls	Active Motile Sperm (%)	Sluggish Motile Sperm (%)	Immotile Sperm (%)	Progressive Motile Count (Million/Ejaculate)
Controls	51.50 $\pm$ 1.59 a	31.16 $\pm$ 0.94	17.33 $\pm$ 1.21 a	91.10 $\pm$ 20.97 a
Patients before treatment	30.11 $\pm$ 2.52 b	33.44 $\pm$ 1.85	36.44 $\pm$ 3.51 b	18.02 $\pm$ 2.40 b
1 Month after treatment	30.66 $\pm$ 2.58	35.00 $\pm$ 1.74	34.33 $\pm$ 3.24	23.88 $\pm$ 3.82
2 Month after treatment	33.55 $\pm$ 2.42 *	34.44 $\pm$ 1.48	32.00 $\pm$ 2.94 *	27.42 $\pm$ 4.09 *
3 Month after treatment	35.77 $\pm$ 2.70 *	34.77 $\pm$ 1.55	29.44 $\pm$ 3.30 *	33.22 $\pm$ 4.77 *

\* $p < 0.05$  represents significant difference between before treatment and after treatment. Different letters represent significant difference between controls and the patients before treatment.

**Group B patients****Table 3: Effects of L-carnitine and multivitamins treatment on the mean  $\pm$  SE of seminal fluid volume, sperm concentration, and sperm count in idiopathic infertile patients(n=55) compared to controls (n=30).**

Patients/Controls	Seminal Fluid Volume (ml)	Sperm Concentration (Million/ml)	Sperm Count (Million /Ejaculate)
Controls	2.63 $\pm$ 0.13	63.26 $\pm$ 10.08 a	168.96 $\pm$ 31.82 a
Patients before treatment	2.48 $\pm$ 0.14	12.96 $\pm$ 1.13 b	30.58 $\pm$ 2.86 b
1 Month after treatment	2.52 $\pm$ 0.12	18.41 $\pm$ 1.65 *	44.98 $\pm$ 4.43 *
2 Month after treatment	2.48 $\pm$ 0.10	20.07 $\pm$ 1.50 *	51.05 $\pm$ 4.58 *
3 Month after treatment	2.45 $\pm$ 0.08	22.43 $\pm$ 1.57 *	54.99 $\pm$ 4.30 *

\*p<0.05 represents significant difference between before treatment and after treatment. Different letters represent significant difference between controls and the patients before treatment

**Table 4: Effects of L-carnitine and multivitamins treatment on the mean  $\pm$  SE of sperm motility (represented as percent of total) in idiopathic infertile patients(n=55) compared to controls (n=30).**

Patients/Controls	Active Motile Sperm(%)	Sluggish Motile Sperm(%)	Immotile Sperm (%)	Progressive Motile Count (Million /Ejaculate)
Controls	51.50 $\pm$ 1.59 a	31.16 $\pm$ 0.94	17.33 $\pm$ 1.21 a	91.10 $\pm$ 20.97 a
Patients before treatment	22.81 $\pm$ 2.22 b	32.58 $\pm$ 1.77	44.60 $\pm$ 3.18 b	8.02 $\pm$ 1.05 b
1 Month after treatment	25.63 $\pm$ 2.20	34.36 $\pm$ 1.39	40.18 $\pm$ 2.84	13.40 $\pm$ 2.03 *
2 Month after treatment	26.63 $\pm$ 2.02 *	36.00 $\pm$ 1.17 *	37.34 $\pm$ 2.42 *	15.15 $\pm$ 1.96 *
3 Month after treatment	29.36 $\pm$ 2.27 *	35.81 $\pm$ 1.46	34.90 $\pm$ 3.15 *	18.03 $\pm$ 2.19 *

\*p<0.05 represents significant difference between before treatment and after treatment. Different letters represent significant difference between controls and the patients before treatment

**Table 5: Effects of multivitamins treatment on the mean  $\pm$  SE of seminal fluid volume, sperm concentration, and sperm count in idiopathic infertile patients(n=29) compared to controls (n=30).**

Patients/Controls	Seminal Fluid Volume (ml)	Sperm Concentration (Million/MI)	Sperm Count (Million/ Ejaculate)
Controls	2.63 $\pm$ 0.13	63.26 $\pm$ 10.08 a	168.96 $\pm$ 31.82 a
Patients before treatment	2.43 $\pm$ 0.17	20.37 $\pm$ 1.11 b	47.68 $\pm$ 3.61 b
1 Month after treatment	2.39 $\pm$ 0.14	22.37 $\pm$ 1.31 *	52.72 $\pm$ 4.44
2 Month after treatment	2.46 $\pm$ 0.14	23.89 $\pm$ 1.78 *	57.68 $\pm$ 4.97 *
3 Month after treatment	2.50 $\pm$ 0.11	24.72 $\pm$ 1.70 *	62.17 $\pm$ 5.29 *

\*p<0.05 represents significant difference between before treatment and after treatment. Different letters represent significant difference between controls and the patients before treatment

**Table 6: Effects of multivitamins treatment on the mean  $\pm$  SE of sperm motility (represented as percent of total) in idiopathic infertile patients(n=29) compared to controls (n=30).**

Patients/ Controls	Active Motile Sperm (%)	Sluggish Motile Sperm (%)	Immotile Sperm (%)	Progressive Motile Count (Million/ Ejaculate)
Controls	51.50 $\pm$ 1.59	31.16 $\pm$ 0.94	17.33 $\pm$ 1.21	91.10 $\pm$ 20.97 a
Patients before treatment	46.06 $\pm$ 1.47	34.24 $\pm$ 1.39	19.68 $\pm$ 1.65	21.81 $\pm$ 1.66 b
1 Month after treatment	45.68 $\pm$ 1.12	33.96 $\pm$ 1.39	20.34 $\pm$ 1.40	24.29 $\pm$ 2.28
2 Months after treatment	46.03 $\pm$ 1.43	34.13 $\pm$ 1.26	19.82 $\pm$ 1.45	26.52 $\pm$ 2.58 *
3 Months after treatment	46.89 $\pm$ 1.72	33.44 $\pm$ 1.21	19.65 $\pm$ 1.71	29.29 $\pm$ 3.19 *

\*p<0.05 represents significant difference between before treatment and after treatment. Different letters represent significant difference between controls and the patients before treatment

**Table 7: Percentages of increase in sperm concentration, sperm count, actively motile sperm, and progressive motile sperm count measured after 3 months of treatment when compared with their corresponding values before treatment in group A, B, and C patients.**

Parameter measured	Percentage of increase in the semen parameters measured after 3 months when compared with values before treatment		
	Group A patients	Group B patients	Group C patients
Sperm concentration	54%	73%	21%
Sperm count	60%	80%	30%
Active sperm motility	19%	29%	Non Significant (NS)
Progressive motile sperm count	84%	125%	34%

No significant differences were found between the values of round cell count in the patients of different groups before and after treatment and those of the control subjects.

The above results had demonstrated that L-carnitine at a daily dose of 2 gm/day for a treatment period of 3 months can improve sperm concentration, sperm count, percentage of actively motile sperm, and progressive motile sperm count among men with idiopathic oligo- and/or asthenozoospermia, and the combination of L-carnitine and multivitamins for the same period of treatment is more efficient than either L-carnitine or multivitamins alone (in the form of Stresstabs®) for the improvement in these semen parameters and can aid in the treatment of idiopathic male infertility. In addition, L-carnitine may be better than the use of oral multivitamins in the dosage regimens applied in this study in improving semen parameters and treatment of idiopathic male infertility. Moreover, the use of the progressive motile sperm count in the seminal fluid analysis is more indicative for the improvement in semen parameters than the sperm count and percentage of actively motile sperms separately, since it represents the product of multiplying the sperm count by the percentage of actively motile sperm.

## Discussion

Other similar studies have suggested an improvement in semen parameters of men with low sperm motility following treatment with oral carnitine<sup>(14, 15, 2)</sup>. These observations suggest a role of carnitine or acetylcarnitine as empiric therapy for idiopathic asthenospermia<sup>(16)</sup>. The significant effect of L-carnitine on increasing sperm concentration, sperm count, and percentage of actively motile sperm in this study could be due to or explained by of which is that L-carnitine is an essential cofactor that could accelerate lipid metabolism and has a pivotal role in mitochondrial  $\beta$ -oxidation of long-chain fatty acids for cellular energy production<sup>(4,5)</sup>. There is also an unknown effect of L-carnitine in Sertoli cell-

spermatogenic line interaction, an action on the postmeiotic phases of spermatogenesis (for example, on the chromatin stability or mitochondrial function of spermatocytes or spermatids), or an improvement in the quality of the epididymal microenvironment, reducing gamete phagocytosis at this level while increasing ejaculated spermatozoa<sup>(17)</sup>. In addition, carnitine administration increases prostaglandin E2 concentration<sup>(18)</sup>, which affects sperm count<sup>(19)</sup>. Moreover, carnitine protects cell membrane and DNA against damage induced by free oxygen radicals. It also prevents protein oxidation and lactate oxidative damage<sup>(20, 9)</sup>. Hence, it acts as an "anti-aging" substance, protecting against damage induced by free oxygen radicals<sup>(17)</sup>. In the same manner, there was a significant increase in the progressive motile sperm count, since it is a product of sperm count and the percentage of active motile sperm. A number of studies have suggested a beneficial role of antioxidants or anti-ROS drugs (vitamin E, vitamin C and GSH), including improved sperm quality and increasing fertilizing capacity<sup>(3)</sup>. Vitamin E is one of the major membrane protectants against ROS and lipid peroxidation<sup>(21)</sup>. Because vitamin E is a chain-breaking antioxidant and not a scavenging antioxidant, it would be expected to offer protection to membrane components without influencing ROS generation<sup>(22)</sup>. Vitamin E, on the other hand, acted as an effective antioxidant and significantly enhanced the capacity of human spermatozoa for sperm-oocyte fusion. Vitamin B12 and folic acid are important in cellular replication, especially for the synthesis of RNA and DNA, and deficiency states have been associated with decreased sperm count and motility<sup>(23)</sup>. Vitamins B1, B2, B3, B5, and B6 are important in many metabolic pathways in cells in general (and sperm in particular), and any deficiency in these vitamins can lead to defects in sperm metabolism and normal

functions<sup>(24)</sup>. Although pregnancy was not a principal end point in many studies<sup>(15, 14)</sup>, including this study, as it is difficult to avoid the many confounding variables acting on naturally induced fertilization and subsequent pregnancy, one pregnancy was recorded in group B patients after 2 months of treatment. In conclusion the present study had demonstrated that L-carnitine at a daily dose of 2 gm/day for a treatment period of 3 months can improve sperm concentration, sperm count, percentage of actively motile sperm, and progressive motile sperm count among men with idiopathic oligo- and/or asthenozoospermia, and the combination of L-carnitine and multivitamins for the same period of treatment is more efficient than either L-carnitine or multivitamins alone

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