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The impact of L-carnitine Supplement on Semen Variables and the Levels of Sexual Hormones (Serum LH, FSH, Testosterone, and Inhibin) in Males with Infertility

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Abstract

Background: It had been estimated that tenth of partners had infertility, and in approximately half of these cases, the imperfection can be ascribed to male related causes. Fecundity in men necessitate regular functioning hypothalamus, pituitary gland, and testes axis. aberrant spermatogenesis is habitually incorporated to permuted serum gonadotropins and testosterone. L-carnitine is an supreme antioxidant existing in a lofty concentration in epididymal excretions. It affords liveliness for sperms to earn their dynamism in the epididymis.

Aim: The study proposed to explore the effect of L-carnitine supplement on semen parameters, and sex hormones milieu in patients with primary or secondary infertility.

Patients and Methods: A clinical trial conducted on a 58 patients(mean age± SD: 30.6 ± 6.07) treated with 2gm of L carnitine, which prescribed orally at a daily dose of 2gm a day in divided doses for 3 months. Before, and after the end of the L-carnitine treatment, semen analysis and serum levels of LH, FSH, Testosterone, and inhibin were performed.

Results: The mean values of sperm count, total motility and normal morphology of and oligo-astheno-teratospermic were found notably changed ($p<0.05$) with 3 months carnitine supplement. The outcome of this trial exhibited that L-carnitine supplement can improve sperm concentration, and count, as well active motility. Additionally it has been noticed that the serum gonadotropin (FSH and LH) levels were noteworthy declined, while serum testosterone and inhibin levels were upraised in infertile males when compared with the levels before, the 3 months course of L-carnitine treatment.

Keywords: *L.Carnitne, semen variables, sex hormones, OAT.*

Introduction

Infertility is a failure to procure conceiving over a year of orderly unguarded coitus. It affects nearly 15% of sexually active partners; however, male factor accords to up to 40% of instances [(1)]. The male aspects of aberration marked by decrease sperm tally and/or sperm motility and/or raised anomalous sperm morphology. These changes are altogether named oligo-astheno-terato-zoospermia (OAT) and they are regarded noteworthy only if discovered in 2 sequential perusals of semen samples collected apart within one to four weeks. This accordant with the WHO guidelines (2010) [(2)]. Around 30% of sufferer have idiopathic (iOAT), which may be linked to aging or to non-inflammatory, or functional changes in epididymis or due to some viral or chlamydial infections [(3-4)] .

Semen analysis prevails the most trustworthy laboratory workup for the assessment of non-fertile male.[5] The remarkable elements that takes primacy in in-vivo and in-vitro fertilization are sperm total number

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and the percent of motile and morphologically normal sperms.[6-7] furthermore, experiences suggested that computer-assisted semen analysis (CASA) exactly and trustably evaluate kinematics of the sperms, which sequentially, highly related to the fertility rate in-vitro and in-vivo time to conceive.[8-9]

The therapy of male infertility particularly iOAT can be burdensome. Many medicines, dietary supplementations and antioxidants are tried but a verifying evidence reinforcing their efficacy is not yet proved [(10)] .

L. carnitine (LC) is a water-soluble, and a vitamin-like structured molecule. Three quarters of the body requirments of LC is of dietary source and only 25% is endogenously synthesized from lysine and methionine the two essential amino acids, and they are hoarded in striated muscles, cardiac muscles, brain tisues, and testicles.[(11)] The lofty level of LC is detected in epididymal excretions and sperm, with a level of about 2000 folds higher than that of the plasma giving a clue about its pivotal task in energy metabolism and sperm maturation.[12] Furthermore, LC convey the long-chain fatty acids from the cytosol into mitochondria and promote β-oxidation of long-chain fatty acids so it plays vital role in energy production.[13,14] LC have an essential duty as it act as an outsized non-enzymatic antioxidant and helps in cell, mitochondrial membrane, and DNA protection against structural disfigurement induced by oxygen free radicals. Many experiments have been conducted to assess the antioxidant role of carnitine, their results demonstrate upswing of antioxidant enzyme activities, and the curtailment of oxidative stress in diverse cells. [15]

The balanced endocrine interplay of hypothalamus, pituitary and the testis, determine the flourishing and utter development of male gametes. Hypothalamus excreted gonadotropin releasing hormone (Gnrh) evoke the libration of gonadotrophins i.e follicle stimulating hormone(FSH) and lutenizing hormone(LH) from the pituitary gland [(16)]. FSH ties up with the sertoli cells receptors, and triggers spermatozoa production. LH triggers the excreation of testosterone in Lydge cells, which seriatimly exploit on the Sertoli and peritubular cells of the seminiferous tubules and trigger spermatozoa production [(17)]. The failed secretion of FSH and LH by the hypophyseal stalk will result in turmoil of testicular function causing infertility. Testosterone, estradiol as well as inhibin orchestrate the excretion of gonadotropins [(18)]. The upraised FSH level in men with azoospermia or severe oligospermia (less than 5million sperm/ml) stipulate seminiferous tubules damage [(19)]. Moreover if inhibin, testosterone, dihydrotestosterone and estradiol secretion is changed, this will disorganize the negative feedback mechanism which lead to disturbance of the levels of FSH [(20)]. Customarily, the amount of FSH correspond to the production of sperms, when spermatogonia are non-existent or strikingly reduced, FSH level will be skywarded ; when the quantity of spermatogonia within normal limits, but their maturation is arrested at a specific stage (spermatocyte or spermatid), FSH values are in the ordinary range.[(21)]

The study proposed to explore the effect of L-carnitine supplement on semen parameters, and sex hormones milieu (serum LH, FSH, Testosterone, and Inhibin levels) in patients with primary or secondary infertility.

Patients and Method

A clinical trial conducted between November 2016 to the end of December 2018, a total number of 82 infertile male patients (aged 18-47 years) referred to the infertility clinic in Salahaldeen General Hospital, after the exclusion of 15 patients with varicocele, orchitis, cryptorchidism, and those males who taking herbals or medications that might affect seminal parameters in the last 3 months prior to the study, and 9 patient dropped out because of incompliance of treatment; 58 treated with L-carnitine 2 mg given orally in 2 divided doses a day. The treatment period was 3 months. Seminal fluid analysis and serum levels of LH, FSH, testosterone, and inhibin, was done prior to the onset of the study and after the end of the treatment course. Semen samples were collected after 3-5 days of sexual abstinence and the standard manual semen analysis was performed according to the WHO guidelines [(2)] . During the study period, the patients were interviewed monthly to assess their compliance with treatment.

Infertility assigned depending upon (WHO) guidelines. Infertile males, with more than 1year infertility, in spite of regular coitus with a normal female partner were chosen. The diagnosis was made after clinical assessment that includes: history; clinical examination especially for varicocelle and testicular volume which further evaluated by sonography of genitalia. Semen analysis; Follicular stimulating Hormones (FSH), Leutinizing Hormone(LH), testosterone, and inhibin

levels were done for each patient before and after treatment course. The semen parameters, including sperm concentration, total and forward sperm motility (percentage at one hour after ejaculation) and sperm morphology (percentage of atypical forms), according to WHO standard procedures. Data presented with simple tables and analyzed statistically to test significance at p value< 0.05

Result

In this prospective study we considered a total of 58 patients with infertility due to unexplained astheno, oligo, and/or teratospermia before and after treatment with L. carnitine for 3 months. The mean age was 29.7 ± 5.07 years. The mean duration of infertility was 3.9 ± 4.65 (1.5 to 11years). 58 patients given L carnitine for three months. The median seminal fluid volume, total perm count, normal appearance, the actively motile and Viabile sperm percentage of the treatment group before treatment were 2.1 *vs.* 3.1ml, 21 *vs.* 41million ,21% *vs.* 51% , 28% *vs.* 47% and 36% *vs.* 72% respectively, which a noteworthy increment (P<0.05).

Additionally a significant drop in sluggish and non-motile sperm percentage, as well the teratospermia percentage (47% *vs.* 23%, 43% *vs.* 26% and 58% *vs.* 29% respectively) was beheld. (P<0.05).

Table (1): Semen parameters before and after 3months treatment with L. carnitine

Parameters	Mean ± S.D. before	Mean ± S.D. after
Volume (ml)	2.10±0.39	3.12±0.74*
Count	21±2.3546	41±3.7651*
Active	28±5.887	47±6.4 16*
Sluggish	47±5.226	23±3.709*
Non Motile	43±5.472	26±3.756*
Normal	21±4.561	51±5.103*
Abnormal	58±5.082	29±4.110*
Viability	36.88±12.31	72.7±5.2*

P value<0.05

As it is clear in table 2, after 3 months of 2gm of L-carnitine for the selected infertile patient with hypofertility, a significant decline in the serum levels of gonadotropins(FSH, LH) 9 vs. 5 IU/L, and 6 vs. 4 IU/L respectively. On the other hand, a notable elevation in serum testosterone and inhibin B levels (4 vs. 7 ng/ml and 99 vs. 232 pg/ml respectively) have been recorded.

Table (2): Hormonal assay before and after 3months treatment with L. carnitine

	Before L-carnitine	After L. carnitine
FSH (IU/L)	9.534(±1.418)	5.650(±0.721)*
LH (IU/L)	6.346(± 9.112)	4.234(±1.109)*
Testosterone ng/ml	4.556(±1.167)	7.122(± 0.571)*
Inhibin B pg/ml	99.436(±6.472)	232.756(±5.945)*

P value<0.05

Discussion

In the near past time, male has not been accused as a cause of infertility. Male hypo-fertility has no distinct existence but it displays a diversity of pathophysiologic mechanisms. Sperms in the environment of Epididymis use a various substrates as sources of energy, but oxidation of fatty-acid which involves carnitine dependent system appears to be the crucial energy vouchsafing operation[22].

Mazzilli et al divulged a solid relation between spermatic cytoplasmic L-carnitine reserve with spermatic activity and viability in the mucus of uterine cervix of bovine. This correlation could be described by the fact that fats are prime energy resource for sperms in cervical mucus blug and to utilize these fats, it is important to have adequate cytoplasmic spermatic L-carnitine. L-carnitine not only aids in metabolism of lipids, but it adjusts the hoards of the free CoA as well, which is vital for tri-carboxylic acid cycle adjustment. That's why , L-carnitine reserves can be regarded as an index of spermatic activity extent in cervical mucus.[23]

The refinement in the fertility tally achieved by L-carnitine supplement allocated by the noteworthy upgrading in sperm concentration and total counting, volume of ejaculate and proportion of highly motile spermatozoa in our trial could be explained by the inkling

that L-carnitine is a vital cofactor that may enhance lipid metabolism and play a crucial role in mitochondrial beta-oxidation of long-chain fatty acids for cell life maintenance and energy production. (24,25)

A controlled trial conducted in (2004) by Lenzi et al. written account of a noteworthy relations between LC/LAC and ameliorations in all semenal indices in 56 infertile males with unexplained Oligo-Astheno-Spermia who treated by 2 g/day of LC and 1 g/day of L-acetyl carnitine (LAC) for a 180 days duration.26) An observational study of infertile men conducted by Haseen and his team research in (2017) approved that free LC seminal proportions were further down in hypo-fertile male than in control group, and a sturdy positive relations were noticed between semen plasma LC proportions and sperm number, activity, and normal morphology .(41)

A randomized trial conducted by Ramesh Babu and his team in (2004), described an increment with significant differences ($p< 0.05$) in the mean FSH and LH levels in all of non-fertile males studied when compared with the control arm of the study. Though, difference in the mean levels of testosterone in both arms was insignificant.(28) Reports as early as (1994) demonstrated by Zabul and followers when they established that gonadotropin (FSH and LH) levels were significantly higher in non-fertile men in comparism to the levels in controls with proved fertility. (29)

FSH is mandatory for initiation of production and evolution of spermatozoa. FSH is regarded as a reliable marker of damage of germinal epithelium, so it's found in higher concentration, in the sera of hypo-fertile men, and it was shown that this elevation is associated with azoospermia and severe oligozoospermia.(19)

Upswing of seminal fluid indices, after 3 months of 2gm daily dose of L-carnitine that has been noticed in our trial suggesting the boosted spermatogenesis and maturation of spermatozoa that seemed to be governed by the antioxidant power of L-carnitine, and by enhanced level of serum testosterone. While the induced spermatogenesis, and increased levels of serum testosterone and inhibin hormones may be the stand behind factors that resulted in reduction of LH and FSH hormones levels by its negative feedback effects.

Conflict of Interest - (nil – There are "No Conflict of Interest")**.**

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Ethical Clearance: Committee members are approved to perform a study about "The impact of L-carnitine supplement on semen variables and the levels of sexual hormones (Serum LH, FSH, Testosterone, and Inhibin) in males with infertility" after discussion of study plan with researchers.

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