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Cancer Induced Infertility and the Role of L-Carnitine: A Review for Possible Future Clinical Applications

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Abstract

Context: Epididymis is highly rich by L-carnitine (LC), which serves as a protectant agent for the oxidation process and also has key roles in energy production and motility enhancement. Progress in cancer survivor beside dramatic increase in cancer prevalence has led to universal interest for fertility preservation in survival of patients with cancer. Recently, a trend is established for evaluating the effects of LC and its ester supplementation on radio and chemotherapy induced gonadal injury. This article focused on chemotherapy induced infertility, mechanisms involved, and the possible protective role of LC.
Evidence Acquisition: All papers including clinical trials, case reports, case series, and reviews on the role of LC in the cancer induced infertility were obtained by searching in medical publications such as Elsevier, PubMed, Google Scholar, and clinical trials.
Results: L-carnitine pre-treatment was effective in improving sperm parameters, especially total motility, viability, reducing cell apoptosis; it was also able to promote the quality of the semen exacerbated by chemotherapy agents such as etoposide, doxorubicin, and cyclophosphamide in animal model.
Conclusions: According to animal studies, the administration of LC could show a promising protective data, but before any judgment, further large controlled studies are required and issue is matter of concern in future studies.

Keywords: L-Carnitine, Epididymis, Infertility, Gonadotoxicity, Cancer, Chemotherapy

1. Context

1.1. Cancer Induced Infertility

The significant increase in long-term survival of patients with cancer beside the dramatic increase in cancer prevalence has led to universal interest for fertility preservation in survival of patients with cancer. Nowadays, the protection against iatrogenic infertility caused by gonadotoxic chemo and radiotherapy is putting in high priority concern (1, 2). Critchley et al. (3) estimated that 1 in a 1000 young woman aged less than 35 years have been cured of cancer, however; their future fertility might be affected by treatment modality.

However, cancer treatment leads to infertility in both men and women; avoiding the infertility is more considerable in women; hence, women mostly encounter to pre-mature ovarian failure (POF) due to follicular damage (4). For example, it is reported that among women more than 25 years and less than 25 years old, who have received mechlorethamine, vincristine, procarbazine, and prednisone (MOPP regimen), about 50% and 20%, respectively, will experience POF (5).

Unfortunately, one of the most devastating long-term adverse effects of chemotherapy administration for cancer treatment, especially lymphoma and leukemia, is infertility induction (6).

Cancer survivors often concern about the impact of cancer or its treatment on offspring conceived and pregnancy outcome. Increasing in risk for malignancy, congenital anomalies, and growth arrest are the most important items for concerning.

In fact, the mechanism reported for cancer induced infertility is insult inserted to the hypothalamic-pituitary-gonadal axis, as well as direct toxic effect on reproductive organs. The administration of cytotoxic drugs, treatment with radiation, applying surgery, and the disease process per se can lead to temporary or permanent infertility (6). Chemotherapy induced damage in ovaries is irreversible because the germ cells' number is fixed from prenatal life (7-9).

The type and stage of cancer, the cumulative dose of chemotherapy drugs and radiotherapy, the extent of surgical therapy, age, gender, and genetic factor make the mag-

nitude of infertility risk.

There is a large cohort study, which was assessing Canadian and American statistical centers for finding the risk of infertility among younger than 21 years old cancer survivors with eligible malignancy. In this study, fertility rate was compared between female cancer survivors and partners of male cancer survivors with their matched sibling (8-12). Several major findings have been released, stating that the relative risk of a pregnancy was lower among female survivors than their matched siblings (8). Also, male cancer survivors were less likely to fertile the partner than their siblings (8). An increased risk of clinical infertility was seen among female survivors compared with their sibling that was most prominent at early reproductive ages (12).

Both female survivors and siblings had equal rate of seeking for infertility treatment, but the rate of prescribed drugs was less for female survivors. The reported risk factors for infertility induction were cumulative doses of radiation to uterine and administration of alkylating agents in chemotherapy regimen. Although the cumulative time for getting pregnant in cancer survivors was longer than their siblings, more than 60% of 455 infertile cancer survivors' participants were eventually conceived. Unfortunately, the risk of nonsurgical premature menopause female survivors was higher in female cancer survivors than their siblings (10).

Furthermore, fertility preservation is a matter of concern in affected patients with cancer. It has been noted that, feeling of being a good and healthy parent is one of the strongest reasons of emotional well-being, happiness, and life accomplishment among cancer survivors.

The exact mechanism of gonadotoxic effect of various chemotherapeutic agents is still unclear; interference in cellular processes and cell proliferation has been suggested depending on woman's age, chemotherapeutic regimen, and ovarian reserve (6).

Being completely different from gametogenesis in the testis, follicles in the ovaries are progressively lost with increasing age. Depletion of oocyte will be accelerated during chemotherapy and radiotherapy resulted in premature menopause in cancer survivors (13, 14). Due to more amounts of oocytes in younger woman, gonadal toxicity assumes to be less vigorous in comparison with older patients.

Among chemotherapy agents, the most severe direct effects on oocyte destruction and follicular evacuation have been reported by the administration of alkylating agents. Additionally, cortical fibrosis, ovarian atrophy, and blood-vessel damage are noted (7).

Gonadotoxicity and female-specific mutagenic effects have been reported after the administration of platinum agents, as well (6, 15). It is thought that embryotoxicity by these agents is due to chromosomal abnormalities and the induction of dyskarriosis, such as deletions, translocation, and DNA rearrangements (16).

The sensitivity of gonads to irradiation therapy is high and completely affected by the field of treatment, cumulative dose, and administration schedule (17).

Even the low dose of radiation therapy (e.g. 0.1 - 1.2 Gy) can disturb spermatogenesis in male patients with cancer, even though permanent damage was seen in doses of more than 4 Gy (18). Several modalities in both genders were applied. Cancer itself is also charged of inducing gonadal dysfunction. For instance, up to 70% of male patients suffering from Hodgkin's disease had impaired semen quality before induction regimen (19). During Hodgkin's disease treatment, the combination of alkylating agents, such as procarbazine, chlorambucil, chlormethine, and cyclophosphamide may be used. These combination agents have remarkably increased overall survival, but on the other hand, they will be led to permanent azoospermia in most of male patients receiving chemotherapy (20).

Totally, fertility preservation has been accomplished by shielding gonads during radiation therapy and having some consideration for minimal resection during surgery when it is possible. Today, several investigational and modern practical methods of fertility preservation have been applied. Among them, cryopreservation of embryos or oocytes in woman and sperm in woman are proved approaches. Pre-treatment with gonadotropin-releasing hormone (GnRH) agonists, cryopreservation of ovarian, and auto-transplantation of gonadal tissue are the most controversial subjects and the active areas of investigation (6, 7).

2. Evidence Acquisition

All papers including clinical trials, case reports, case series, and reviews on the role of LC in the cancer induced infertility were obtained by searching in medical publications, such as Elsevier, PubMed, and clinical trials.

3. Results

3.1. L-Carnitine and Infertility

L-carnitine (LC) (g-trimethylamino-b-hydroxybutyrate) is an essential quaternary amine exists naturally in mammalian cells. Its effects were exerted by playing an important role in long-chain fatty acids transferring across the mitochondrial membranes, leading to facilitation in oxidation process in mitochondria and energy generation (21). Since a century, the beneficial

effects of LC and its derivatives on the human organism are known.

Despite some known high energy consumption tissues such as skeletal and cardiac muscles which are rich by LC, this agent is highly concentrated in the epididymis as well. As a reproductive tissue, the presence of LC is related to its possible role in functional capacity, energy metabolism, and maturation of spermatozoa.

In the epididymis, free LC is absorbed from the circulating blood and, then, transported by using a specific carrier under the regulation of androgens through the epithelial cells. L-carnitine is, then, accumulated in epididymal plasma and spermatozoa nearly 2000-fold greater than circulating levels.

The main source of energy metabolism in epididymal spermatozoa is fatty acid oxidation. So, the role of LC in fatty acid transportation into the sperm mitochondrial matrix for energy production is vital. L-carnitine plays an important role in intramitochondrial acyl group transportation, and in the form of acyl CoA, it acts as a substrate for β-oxidation metabolism (22).

In a recent study, the administration of LC and its derivative, L-acetylcarnitine, alone or in combination led to a dose-dependent decrease in Sertoli cell amino acid conjunction. It can also enhance the mRNA expression of the glucose transporter (Glut-1) and reduce IGF binding protein-4 (IGFBP-4). The action suggests that LC plays a role in Sertoli cells function and male fertility era (23).

Additionally, it has been noted that LC has direct collaboration in sperm motility and maturation. Its potential clinical application is to increase sperm motility in patients with asthenozoospermia (22).

For example, Balercia et al. designed a trial in 60 patients affected by idiopathic asthenozoospermia. The patients were administrated by either LC 3 g/day, acetyl-L-carnitine 3 g/day, or a combination of the 2 agents for 6 months. Results showed that acetyl-L-carnitine alone and especially in combination resulted in the improvement of sperm motility after 3 months. In addition, amelioration in total oxyradical scavenging capacity of the seminal fluid in treated patients was seen (24). In a similar manner, De Rosa et al. recruited 170 infertile men and divided them into 2 groups according to sperm motility defined by World Health Organization (WHO) (higher or lower than 50%). Further classification was done in patients with total sperm motility < 50% including 2 further groups: group 1A men without azoospermia; group 1B men with primary or secondary azoospermia. The group 1A has received LC 1 g/day and acetyl-L-carnitine 500 mg twice daily for 6 months; at the end of study, the results showed that conventional and non-conventional sperm parameters have been improved (25).

One of the major reasons of losing male fertility is inflammation in urogenital tract, such as epididymitis or inflammation in epididymis. Some studies have proved that LC concentration will be reduced in the seminal fluid during epididymitis (26, 27). Under inflammatory condition, the overproduction of reactive oxygen species (ROS) from leukocyte and/or spermatozoa and increase in oxidative stress could lead to fertility reduction.

Repeatedly, the anti-apoptotic effects of LC have been noted in many organs (28). Several in vivo and in vitro studies support this concept in germ cells of testis. Since that, improvement in quality and quantity of spermatozoa was reported in several clinical trials after LC administration (28, 29).

On the other hand, recent studies have postulated that adding LC into a spermatozoa, which is to be incubated, improves sperm's vitality and motility (30). If this claim is supported by other studies, LC supplementation will improve the quality of semen samples considered for cryopreservation and other laboratory fertilization (31).

Erectile dysfunction is one of the aspects of infertility in men. Propionyl-L-carnitine was examined in commercial combination form containing arginine, vitamins B3 for treatment of arterial erectile dysfunction by Vicari et al. co-administration of 100 mg sildenafil with this combination was effective in increasing the bioavailable nitrogen oxide (NO) and reduce ROS. However, this data did not prove the efficacy of propionyl-L-carnitine per se (32).

In a recently published systematic review, the effects of LC and/or L-acetyl-carnitine (LAC) were assessed in male infertility according to available evidences.

Data regarding the role of LC and/or LAC in enhancing the sperm concentration and semen volume is inconclusive. It has been cleared that the administration of LC and/or LAC may be effective in improving pregnancy rate and sperm morphology characteristics in male infertility, but the exact efficacy and related mechanism need to be assessed in further investigations (33).

Taken together, it is well clarified that LC and its esters have potential roles in improving sperm parameters, especially total motility that reduces the levels of ROS in seminal fluid, being able to promote the quality of the semen even in the case of cryopreservation. Therefore, LC supplementation can be a rational and effective therapeutic strategy of male infertility. However, the efficacy still needs to be confirmed in large and well-designed clinical trials.

3.2. L-Carnitine and Chemotherapy Induced Infertility

Recently, a trend is established for evaluating the effects of LC and its ester supplementation on radio and chemotherapy induced gonadal injury. In this article, we

decided to review all documents in this era in order to take advantage of potential clinical trials.

For the first time in 2009, LC was subjected to assess whether it has a protective role in chemotherapy agents induced gonadal toxicity. They examined the efficacy of LC administration in a 120 pre-pubertal male Wistar rats divided into 4 groups of control treated with LC (250 mg/kg), sham-control treated with 0.9% saline solution, and etoposide (40 mg/kg intraperitoneally) or etoposide + LC (250 mg/kg). Etoposide caused abnormality in several testicular morphometric parameters and LC partially protects the testis against etoposide induced spermatogenic damage and protects germ cells against apoptosis. In comparison to etoposide group, co-administration with LC ameliorated histological and histomorphometrical alterations, concentration of spermatozoa, and sperm abnormal morphology. However, the authors thought that proving the injurious effects of etoposide in pre-pubertal condition is the most achieved findings, and the protective effects of LC must be confirmed in further investigation (34).

After that, the same group of authors decided to evaluate the LC impacts on doxorubicin-induced spermatogenic damage. Similar to the previous study, 4 groups of pre-pubertal male Wistar rats were selected and 250 mg/kg LC was administrated 1 hour before doxorubicin (5 mg/kg) treatment. Furthermore, the rats were sacrificed at 64-days age, late puberty, and 100-days age, the best time for sexually maturity. Then, their testes were evaluated for biometric, morphometric, and histopathological characteristics. Results were in favor of LC supplementation. In rat treated with LC in both ages, testicular and spermatic parameters were alleviated. In 64 days-aged rats, density of apoptotic germ cells was lower in LC administration compared with doxorubicin-administrated rats. The sperm DNA fragmentation was also lower in LC-administrated 100 days-aged rats. In conclusion, they thought that LC is able to reduce the late testicular and spermatic damages due to doxorubicin therapy in pre-pubertal rats (35).

Dehghani et al. in 2013 established an animal study to evaluate the possible protective effects of LC and testis homogenized tissue (THT) on the sperm parameters and testis structure in male rats were affected by busulfan treatment. They divided 20 adult male rats into 4 groups. Group I was control, in which rats received a single dose of dimethyl sulfoxide and 1 mL of distilled water intraperitoneally. Group II or busulfan group received a single dose of busulfan (10 mg/kg) intraperitoneally. The group III had daily protocol administration of busulfan plus THT and the group IIII was treated by a single dose of busulfan plus 100 mg/kg/day LC intraperitoneally. LC injection was started from 1 day after busulfan injection and continued for 48 days. After this treatment period, the rats were sacrificed for further evaluation. The results of semen analysis and stereological technique showed that THT treatment were more effective than LC, but both agents caused increase in volume of testis, seminiferous tubule, interstitial tissue volume, germinal epithelium height, count of sperm, and decrease in morphologically abnormal sperm (36).

In a recently published article, the almost same methods of assessing the protective effects of LC in animal model against cyclophosphamide induced male infertility were used.

Similar to previous studies, LC pre-treatment led to significantly increase in sperm motility, viability, and testosterone level exacerbated by cyclophosphamide. The suggestive protective mechanisms were the inhibition of cell apoptosis and the positive effects on autophagy (37).

YÜNCÜ et al. evaluated the effects of the combination of vitamin E and LC against methotrexate induced testis injury in rats model. During 17 days, animals were treated daily by 0.5 mL/kg normal saline, 250 mg/kg vitamin E, or 500 mg/kg LC intraperitoneally. On days 3 and 10 of treatment, 20 mg/kg methotrexate intraperitoneally was added to the experimental group. The combination of these agents caused elevation in malondialdehyde levels and the amelioration in superoxide dismutase levels during histopathological investigation (38).

Table 1 summarized the detail of investigational experiments done in animal model. As shown in Table 1, all the data from animal studies have been released recently.

4. Conclusions

The positive effects of LC and its derivatives were noted in different cancer induced complications. For example, cancer induced fatigue and cachexia was successfully managed by LC. Several clinical studies have mentioned the protective effects of LC and its ester on cachexia due to the treatment of cancers (42, 43). Also, some clinical trials examined the protective effects of LC on anthracyclines related cardiotoxicity (44). Its ester, acetyl L-carnitine, has demonstrated efficacy in chemotherapy induced peripheral neuropathy (45).

Our focus was on the effects of this supplement on the infertility induced by chemotherapy. Since years ago, LC roles were discovered in reproductive system and testis functioned as agent, interfering with energy metabolism, motility, and maturation of spermatozoa. Today, there is a trend toward animal studies that have used this supplement in cancer induced infertility issues.

However, still there is a main concern around dose, route, duration of LC administration, sample size, and method of participants selection in clinical trials of LC therapy. The exact mechanisms for LC beneficial effects on

Table 1. Animal Studies Owing to the Effect of LC on Chemotherapy Induced Testis Injuries and Infertility

Model of Studies	Chemotherapy Regimen	Dose/ Route of Administrated LC	Treatment duration	Results	Ref
120 pre-pubertal male Wistar rats divided into 4 groups: treated with 0.9% saline solution, carnitine, etoposide and carnitine+etoposide	Etoposide	IP inj of 250 mg/kg of LC	8 days (concurrently with etoposide)	Increasing in body weight, testis weight, recovery of the seminiferous epithelium, the seminiferous epithelium height and concentration of spermatozoa	(34)
12 thirty-days-old Wistar rats divided into 4 groups: sham-control, carnitine, doxorubicin, and LC-doxorubicin	Doxorubicin	250 mg/kg LC orally 1h before doxorubicin	Single dose	Reduction in germ cell depletion, the number of apoptotic cells, abnormal spermatozoa, sperm transit time and sperm DNA damage, Increasing in (VvEp[a]) , body and testicular weight, seminiferous epithelium height and tubular diameter, sperm number and daily sperm production.	(35)
20 adult male Spraque-Dawley rats (about 180 ±20 gr)	Busulfan	100 mg/kg/day I.P. injection of LC started 1day after injection of busulfan	48 days (based on spermatogenesis in rats)	No significant change in body weight, testis weight, testis volume, testosterone and estradiol levels, sertoli and leydige cells. But increase in mean of sperm count, increase in normal morphology sperm and length of flagella	(36)
24 Wistar male rats 6-weeks-old and weighting 180-200 gr divided to 3 group	Cyclophosphamide	2.1 mg/kg/day LC orally	3 weeks (with fifty days follow up after treatment)	Protection of sperm degradation, increase the spermatozoon motility rate and activity rate, retard the decrease in testosterone and increase in estradiol level, retard germ cell apoptosis, increase the Beclin[b], and LC3[c] expression	(37)
26 young adult Wistar Albino male rats about 5-6 months old divided to 4 group	Methotrexate	500 mg/kg I.P. injection of LC	17 days treatment anf follow up	No significant change in body and testis weight, interstitial site congestion and sertoli cell vacuolization, Increasing in SOD, Decreasing in MDA, germ cells injuries and Multinucleated giant spermatogenic cells	(38)

Abbreviations: IP, Intraperitoneally; MDA, Malondialdehyde; SOD, Superoxide Dismutase.
[a](VvEp): Mean volume densities of seminiferous epithelium.
[b]Beclin 1: This gene encodes a protein that regulates autophagy, a catabolic process of degradation induced by starvation. The encoded protein is a component of the phosphatidylinositol-3-kinase (PI3K) complex, which mediates vesicle-trafficking processes. This protein is thought to play a role in multiple cellular processes, including tumorigenesis, neurodegeneration, and apoptosis. Alternative splicing results in multiple transcript variants.
[c]LC3: MAP1LC3A (Microtubule-associated proteins 1A/1B light chain 3A) is a kind of human protein, which is encoded by the *MAP1LC3A* gene, an important marker of autophagy (39-41).

spermatogenesis are still unclear. Moreover, the translation of in vitro results to clinical effects remains to be elucidated.

The administration of LC has been noted to be beneficial in radiation induced infertility. In animal model studies, LC could ameliorate morphological changes and germ cell apoptosis in the irradiated rat testis (46). Our data over the potential effects of LC on cancer treatment induced is still in infancy. Future research is needed in the area of in vitro and clinical studies for possible beneficiary effects of LC and its ester. There is paucity of data on the effects of LC on woman infertility and biology.

Yurut-Caloglu et al. investigated the radioprotective efficacies of LC and amifostine against radiation induced acute ovarian damage in mice. Having anti-apoptosis and anti-oxidant properties, this combination was successful

in prevention of follicular damages in female rats (47). Before any decision, more well-designed clinical trials are needed.

Cytotoxic therapy can lead to infertility in survival of patients with cancer. Several modalities have been applied to reduce the chemotherapy induced reproductive system injuries, but none of them were completely effective. According to the animal studies, the administration of LC could show a promising protective data and after having proved in clinical studies, it can be consider an alternative agent for routinely protective modalities.

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Footnotes

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