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Clinical Trial

L-Carnitine supplementation ameliorates serum tumor necrosis factor-alpha and matrix metalloproteinase-3 in knee osteoarthritis women

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Abstract

Seventy-two females with mild to moderate knee osteoarthritis were included in this randomized double-blind placebo-controlled study. Patients in the intervention group (n=36) received L-carnitine supplement (750 mg/day) for two months. L-Carnitine supplementation led to decrease in serum TNF-α and MMP-3 levels significantly in comparison with the baseline ($p<0.001$ and $p<0.001$, respectively) and placebo group ($p<0.001$ and $p=0.03$, respectively). In addition, physician's global assessment of the severity of osteoarthritis decreased significantly in the L-carnitine group ($p<0.001$) and placebo group ($p=0.012$) after supplementation. At the end of the study, a significant difference was observed between the two groups for mean physician's global assessment of the severity of osteoarthritis ($p<0.001$), adjusted for baseline values and duration of osteoarthritis. L-Carnitine supplementation has beneficial effects in reducing inflammatory biomarkers in knee osteoarthritis patients which subsequently leads to the alleviation of disease symptoms.

Introduction

Osteoarthritis is the most prevalent type of inflammatory joint disorder, presented by articular cartilage destruction and periarticular bone changes (Felson, 2004). The prevalence of this disease increases significantly with age (Bellare et al., 2014) and is more prevalent in women than men. Since knee is the joint primarily bearing body weight, it is more often affected by osteoarthritis than other joints (Sowers, 2001).

The underlying mechanisms of cartilage degradation are not completely understood but it has been confirmed that inflammatory mediators are directly involved in the regulation of cartilage degradation (Fernandes et al., 2002). It has been indicated that large number of proteinases are found in the synovial fluid in osteoarthritis. The matrix metalloproteinases (MMPs) seem to play a significant role in joint destruction. The MMPs activity is regulated by modulation of production and/or activation from proenzymes and tissue inhibitors of the MMPs (TIMPs) (Andereya et al., 2006). Osteoarthritic cartilage is characterized by the imbalance between MMPs and TIMPs. It has been revealed that levels of matrix-destructive enzymes such as MMP-1, -3, and -13 increased and those of TIMP-1, a proteinase inhibitor, decreased in osteoarthritis cartilage (Dean et al., 1989; Martel-Pelletier et al., 1994). The inflammatory cytokines interleukin-1-beta (IL-1β) and tumor necrosis factor alpha (TNF-α) have been well established in osteoarthritis pathogenesis and are known to increase the secretion of MMPs and reduce the production of TIMPs (Kapoor et al., 2011).

Relieving pain and stiffness and improving physical function are important objectives of therapy in

osteoarthritis patients (Pendleton et al., 2000). Currently available medication regimens including non-opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) can reduce both pain and inflammation quite effectively, but long-term use of NSAIDs has been found to be associated with high risk for gastrointestinal, heart and renal complications (Phillips and Brasington, 2010; Berenbaum, 2008). Therefore, other effective treatments with more safety are needed.

Recently, non-pharmacological treatments have been studied for the management of osteoarthritis. Dietary supplements are one of the non-pharmacological treatments that attract more attention nowadays and have been studied for controlling osteoarthritis. L-carnitine is a dietary supplement that has gained popularity and was recently reported to be effective in the management of arthritis (Stoppoloni et al., 2013; Bianchi et al., 2014; Geraci et al., 2012; Kolahi et al., 2015). Previous *in vitro* and animal studies demonstrated inhibitory effects of L-carnitine on MMPs expression (Bianchi et al., 2014; Deng et al., 2014). Therefore, in an attempt to find new treatments for decreasing inflammation and consequently relieving symptoms in osteoarthritis, this study was designed to assess the effects of L-carnitine treatment on serum TNF-α and MMP-3 in females with knee osteoarthritis.

Materials and Methods

This study was conducted between November 2013 and December 2014. Sample size calculation was made based on 80% power and an error of 5% to detect the treatment effect of L-carnitine on knee pain. Based on these calculations, a total of 60 individuals were needed. Allowing for 20% dropout over 8 weeks of intervention, the total sample size required for the study was 72 individuals. Inclusion criteria were: Women aged 40–60 years who had mild to moderate bilateral primary knee osteoarthritis according to the American College of Rheumatology criteria (Altman et al., 1986; Massicotte, 2011) and body mass index (BMI) of 25–34.9 kg/m^2. Subjects were selected from the Rheumatology Outpatient Clinic of Tabriz University of Medical Sciences. Subjects who had secondary osteoarthritis (due to a known disorder), surgery, or a joint injection of the target knee within the past 6 months, any serious systematic disease, cardiovascular disease, diabetes mellitus, liver, renal and/or thyroid disorders and any other chronic inflammatory disease, pregnancy and lactation, smoking, alcohol intake, currently taking omega-3-fatty acids (e.g., fish oil) and anti-oxidant supplements, use of NSAIDs two weeks prior to and during the intervention were excluded.

Using a random permuted block procedure (block size 4), women were assigned to two main groups: Experimental group (n=36) received 3 tablets per day of L-carnitine tartrate supplement (750 mg/day), and placebo group (n=36) received 3 tablets per day of placebo. The supplements and placebo tablets were identical in appearance and were obtained from Karen Pharmaceutical and Nutrilife Pharmaceutical Co. (Yazd, Iran). The intervention period was 2 months, and subjects were followed by weekly phone contact during this time. The participants were asked to keep their usual dietary intake and physical activity during the study period. Figure 1 presents a diagram of the study design.

5 mL of venous blood samples was collected after 12 hours overnight fasting twice (At the beginning and at

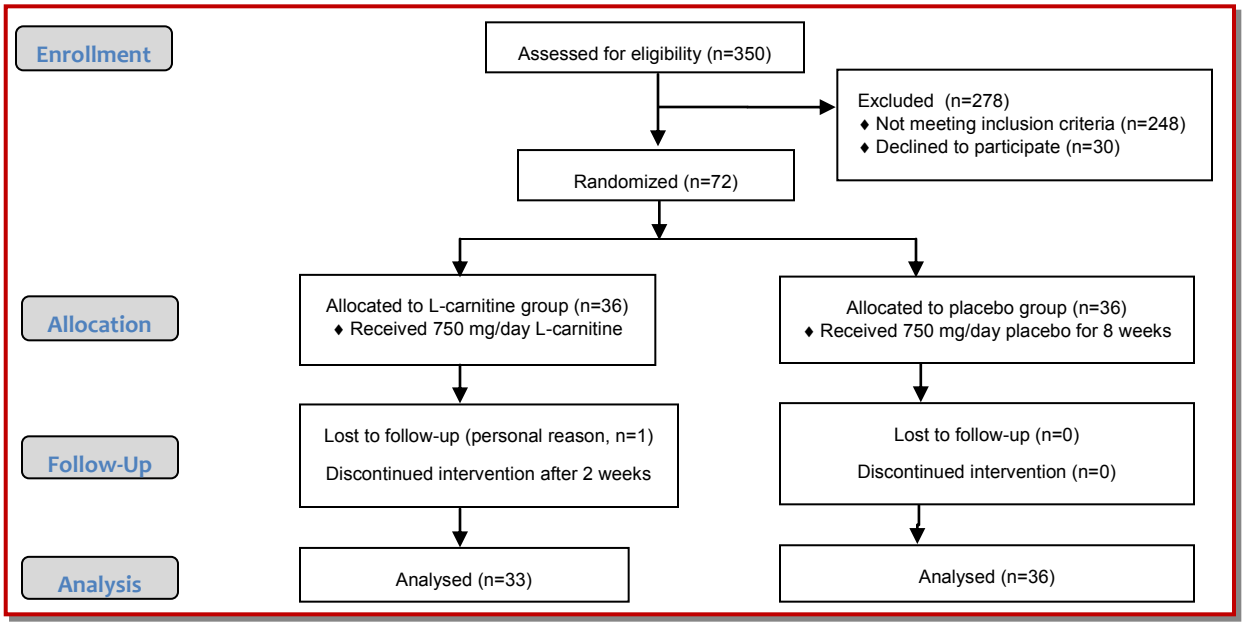

Figure 1: Study flow diagram

the end of the study). Serum TNF-α levels were determined using platinum enzyme-linked immunosorbent assay (ELISA) kits (Orgenium Laboratories, Finland). Serum MMP-3 levels were determined using human ELISA kits from Boster (Boster Biological Technology Co., Ltd., USA). Using an ELISA plate reader (Model Stat Fax 2100, Awareness, USA) at a wavelength of 450 nm, the color changes were measured. All measurements were done following the instructions provided by the manufacturers.

Physician's global evaluation of response to therapy was also measured on a 0- to 100- mm visual analog scale (VAS), was performed, where 0 reveals no symptoms and higher scores indicate more severe the disease (Mehta et al., 2007).

All analysis was performed using SPSS software version 16.0 (SPSS, Inc., USA). Normality of variables distribution was evaluated using the Kolmogorov-Smirnov test. Normally distributed variables were displayed as mean ± standard deviation. Paired t-test was used to compare differences between variables before and after the intervention. Independent sample t -test was used to compare differences between 2 groups. In order to identify differences between the 2 groups at the end of the study, adjusting for baseline values and duration of osteoarthritis, analysis of covariance (ANCOVA) was used. P value less than 0.05 was considered significant.

Results

The mean ± SD age and duration of disease were 51.6 ± 5.7 and 4.1 ± 3.8 years in the L-carnitine group and 52.4 ± 6.6 and 5.8 ± 5.9 years in the placebo group, respectively. As presented in Table I, there were no significant differences between the two studied groups at baseline (p>0.05).

Table II demonstrates serum biochemical parameters before and after intervention in the two studied groups. There were no significant differences between the two groups in terms of serum TNF-α and MMP-3 levels at baseline (p>0.05). Significant decrease was noticed in serum TNF-α levels in the L-carnitine supplemented group (p<0.001), whereas it increased significantly in the placebo group (p=0.010) after the experimental period (Table II). Significant decrease was noticed in serum levels of MMP-3 in the L-carnitine supplemented group (p<0.001), whereas it did not change significantly in the placebo group (p=0.420) after the supplementation period. According to the results of ANCOVA test, there were statistically significant differences between the 2 groups only in serum TNF-α and MMP-3 levels (p<0.05), adjusted for baseline values and duration of osteoarthritis (Table I).

Table I

Baseline characteristics of study subjects

Variable	L-Carnitine group (n = 33)	Placebo group (n = 36)	p value[a]
Age			0.495
40-50 year	12	16	
51-60 year	21	20	
Body mass index			0.445
25-29.9 kg/m²	10	8	
30-34.9 kg/m²	23	28	
Menopause status			0.933
Not menopause	15	16	
Menopause	18	20	

[a]p values indicate comparison between groups at baseline (χ^2 test)

Figure 2 presents the physician's global assessment of the severity of knee osteoarthritis before and after intervention in two groups. At the beginning of the study, there were no significant differences in mean physician's global assessment of the severity of knee osteoarthritis between the 2 groups (p>0.05). In both L-carnitine and placebo groups, physician's global assessment of the severity of knee osteoarthritis decreased significantly (p<0.001 and p=0.012, respectively). According to the results of ANCOVA test,

Table II

Comparison of biochemical variables in treatment groups before and after intervention

Variable	Measurement Period	L-carnitine group (n = 33)	Placebo group (n = 36)	*P*[b]
Serum TNF-α (pg/mL)	Baseline	10.2 ± 7.9	9.2 ± 6.9	0.571
	After 8 weeks	9.1 ± 4.9	10.4 ± 5.4	<0.001
	P[a]	<0.001	0.010	
Serum MMP-3 (pg/mL)	Baseline	29.5 ± 13.3	26.5 ± 9.5	0.291
	After 8 weeks	24.5 ± 12.7	27.7 ± 11.0	0.030
	P[a]	<0.001	0.420	

Data are presented as Mean ± SD; [a]Paired t-test; [b]Independent sample t test at baseline or ANCOVA test, adjusted for baseline values, and duration of osteoarthritis, after 8 weeks

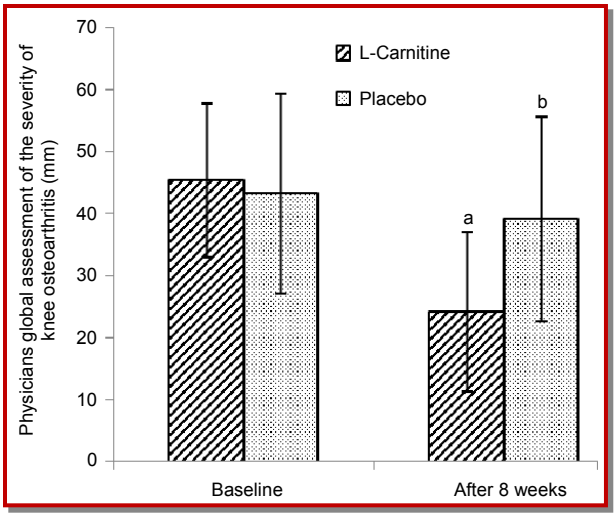

Figure 2. Physician's global assessment of the severity of knee osteoarthritis (100 mm VAS) in the treatment groups at baseline and after 8 weeks. Values are means ± SD (n = 33 in the L-carnitine group and n = 36 in the placebo group). The mean values were significantly different compared with baseline in both groups (paired t-test): [a]p>0.05, [b]p<0.05. The data were tested using independent-sample t test at baseline and ANCOVA test, adjusted for baseline values and duration of osteoarthritis, after 8 weeks

there were statistically significant differences between the 2 groups in mean physician's global assessment of the severity of knee osteoarthritis (p<0.001), adjusted for baseline values and duration of osteoarthritis.

Discussion

It has been indicated that development and progression of osteoarthritis involves inflammation even in the primary phases of the disease. Secreted inflammatory factors such as proinflammatory cytokines are critical mediators of the disturbed metabolism and enhanced catabolism of joint tissue involved in osteoarthritis (Kapoor et al., 2011). Among these cytokines, TNF-α has a key role in inducing apoptosis, inflammation, and matrix destruction through stimulating proteolytic enzyme secretion from chondrocytes and synovial fibroblasts (Aktas et al., 2012). Following this biochemical change, the early inflammatory phase of osteoarthritis occurs (Aktas et al., 2012). Therefore, recent studies are focused on the development of new anti-inflammatory therapeutic approaches particularly dietary supplementation.

According to our results, a significant difference was found between the two treatment groups in serum level changes of TNF-α through the study. L-carnitine has also been reported to have anti-inflammatory characteristic in previous investigations using animal models (Winter et al., 1995; Vescovo et al., 2002; Idrovo et al., 2012; Liu et al., 2011) and human studies, including patients with type 2 diabetes mellitus (Derosa et al., 2011), nonalcoholic steatohepatitis (Malaguarnera et al., 2010), and coronary artery disease (Lee et al., 2014) and patients undergoing hemodialysis (Shakeri et al., 2010; Duranay et al., 2006; Suchitra et al., 2011). Moreover, our results demonstrated a significant difference between the treatment groups in serum level changes of MMP-3 through the study. Similar to our study, Deng et al. (2014) reported that L-carnitine suppressed the production and activity of MMPs induced by hyperosmolarity in primary human corneal epithelial cells.

It has been shown that *in vitro* L-carnitine administration decreased NF-κβ activity, which is responsible for its effects on inducible form of NO synthase (iNOS) expression at transcriptional level. Decreased NF-κβ activity leads to the decrease in iNOS protein expression and nitric oxide synthesis, which has a key role in the pathogenesis of inflammatory diseases (Koc et al., 2011; Moeinian et al., 2013). Furthermore, it has been reported that reactive oxygen species (ROS) may lead to the inflammation which in turn contributes to the increase in expression of proinflammatory cytokines and activation of NF-κβ pathway (Setia and Sanyal, 2012). NF-κB target genes mainly encode regulators of the immune/inflammatory response, such as cytokines, chemokines, and adhesion molecules (Siomek, 2012). According to previous studies, antioxidants could inhibit NF-κβ. Therefore, in present study, L-carnitine inhibited NF-κβ and decreased inflammation by suppressing ROS formation (Conner and Grisham, 1996; Kurutas et al., 2005; Cetinkaya et al., 2006). Hua et al. (2014) indicated that L-carnitine suppressed cyclo-oxygenase II expression and ROS formation in human epithelial cells and thus led to the inhibition of proinflammatory cytokines. Considering the role of cyclo-oxygenase enzymes in producing prostaglandins and thromboxane A2 from arachidonic acid, and the major role of these mediators in developing inflammation and pain in osteoarthritis patients, therefore cyclo-oxygenase inhibition has a major role in decreasing inflammation in osteoarthritis patients (Wittenberg et al., 1993). According to previous findings, levels of leukotriene B4 are increased in osteoarthritis patients which lead to the increase in proinflammatory cytokines. It has been noted that L-carnitine can inhibit lipo-oxygenase enzyme and decrease synthesis of this leukotriene and consequently decrease inflammation (Atik, 1990; Rainsford et al., 1996; Garrelds et al., 1994; Garrelds et al., 1993; Uzuner et al., 2002; Cho et al., 2015).

Our study indicated significant difference between the treatment groups in physician's global assessment of response to therapy through the study. Similar to our study, Bianchi et al. (2014) showed that acetyl-L-carnitine was able to reduce pain in osteoarthritis rat

knee in comparison to the control group. Also, Tastekin et al. (2007) reported that L-carnitine led to the significant improvement in clinical status in rats with adjuvant arthritis. Our findings were consistent with the only similar study carried out by Geraci et al. (2012), in which a food supplement sachet including L-carnitine fumarate (345 mg) improved clinical symptoms significantly in patients with knee osteoarthritis ($p<0.05$). Since inflammation has the key role in etiology of pain and stiffness in osteoarthritis (Cho et al., 2015), supplementation with L-carnitine may improve clinical symptoms by decreasing the inflammatory mediators.

Conclusion

L-carnitine treatment has beneficial effects in reducing inflammatory biomarkers in knee osteoarthritis patients which subsequently leads to alleviation of the disease symptoms.

Ethical Issue

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (Iran) and written fully informed consent was obtained from all trial subjects before participating in the study. The trial has been registered at Iranian Registry of Clinical Trials website (code: IRCT201311231197N17).

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Conflict of Interest

All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work.

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