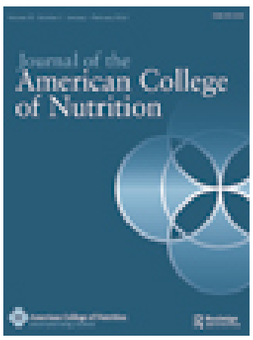

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Original Research

Effects of L-Carnitine Supplementation on Serum Inflammatory Factors and Matrix Metalloproteinase Enzymes in Females with Knee Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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Key words: L-carnitine, inflammation, matrix metalloproteinase, osteoarthritis

Objective: Considering the importance of inflammation in the pathogenesis of osteoarthritis (OA) and induction of pain, this study was aimed to investigate the effect of L-carnitine supplementation on serum inflammatory mediators and OA-associated pain in females with knee OA.

Methods: In this clinical trial, 72 females with mild to moderate knee osteoarthritis started the study, divided into 2 groups to receive 750 mg/day L-carnitine ($n = 36$) or placebo ($n = 36$) for 8 weeks. Serum levels of Interleukine-1β (IL-1β), high-sensitivity C-reactive protein (hs-CRP), matrix metalloproteinases (MMPs)-1 and -13, and visual analog scale (VAS) for pain were assessed before and after supplementation. Data were analyzed by *t* test, Wilcoxon signed rank test, Mann-Whitney U test, and analysis of covariance.

Results: Only 69 patients (33 in the L-carnitine group and 36 in the placebo group) completed the study. L-Carnitine supplementation decreased serum IL-1β and MMP-1 levels significantly ($p = 0.001$ and $p = 0.021$, respectively); however, serum hs-CRP and MMP-13 levels did not change significantly ($p > 0.05$). In the placebo group, serum IL-1β levels increased significantly ($p = 0.011$), whereas other studied biomarkers did not change significantly. The mean VAS score decreased significantly in the L-carnitine and placebo groups by 52.67% and 21.82%, respectively ($p < 0.001$). Significant differences were only observed between the 2 groups in serum IL-1β ($p < 0.001$) and MMP-1 ($p = 0.006$) levels and mean VAS score ($p = 0.002$) after adjusting for baseline values and covariates.

Conclusion: Despite observed beneficial effects of short-term supplementation of L-carnitine in decreasing serum inflammatory mediators and improving pain in knee OA patients, further studies are needed to achieve concise conclusions.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and a major cause of disability among adults, especially in women [1, 2]. Disease progression is associated with cartilage degradation, JSN, and bony changes including osteophytes, subchondral sclerosis, and bone marrow lesions [3]. Knees are more often affected by OA than other joints because the knees are the primary weight-bearing joints [2]. Clinically, pain is the most prominent and disabling symptom of OA, which is associated with functional outcomes and reduced quality of life [4]. Inflammation has been implicated as an important factor in the development and progression of OA and in symptoms such as pain [5–7]. Inflammation and its triggers directly affect

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Abbreviations: ANCOVA = analysis of covariance, BMI = body mass index, COX-2 = cyclooxygenase-2, ECM = extracellular matrix, ELISA = enzyme-linked immunosorbent assay, hs-CRP = high-sensitivity C-reactive protein, IL = interleukin, IL-1Ra = interleukin-1 receptor antagonist, JSN = joint space narrowing, MMP = matrix metalloproteinase, NASH = nonalcoholic steatohepatitis, NSAIDs = nonsteroidal anti-inflammatory drugs, OA = osteoarthritis, TNF-α = tumor necrosis factor-alpha, VAS = visual analog scale.

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synovial cells as well as chondrocytes in the cartilage, causing them to produce cytokines, including interleukin-1-beta (IL-1β) [7–9], and to increase the production of catabolic agents such as proteinases. These mediators consequently affect the destruction of cartilage due to both increased breakdown and impaired repair in order to induce OA and promote pain [10–12]. It has been proposed that the major enzymes responsible for collagen degradation in pathological cartilage are matrix metalloproteinases (MMP)-1 and -13 [13].

Because inflammatory mediators have been associated with the development and progression of OA, anti-inflammatory therapies have commonly been used to treat OA. The most common medications used for the treatment of OA are nonsteroidal anti-inflammatory drugs (NSAIDs; i.e., ibuprofen, diclofenac) or cyclooxygenase-2-specific (COX-2) NSAIDs (i.e., celecoxib) alone or in combination [14]. Many of these treatments have shown limited effectiveness in randomized controlled clinical trials [15–18] and they are associated with an increased risk for cardiac and gastrointestinal complications, particularly with long-term use [19, 20]. Therefore, currently other drugs or supplements without severe side effects may be a preferable option once their efficacy is demonstrable. Dietary supplements have attracted increasing attention and have been studied for the management of OA. L-Carnitine is one of the dietary supplements that has gained popularity and was recently reported to be effective in the management of arthritis [21, 22]. Previous studies in animal models [23–26] and in patients with nonalcoholic steatohepatitis, type 2 diabetes mellitus, coronary artery disease, and patients undergoing hemodialysis [27–31] demonstrated anti-inflammatory effects of L-carnitine supplementation.

To the best of our knowledge, there is no study investigating the effects of L-carnitine on inflammatory response in OA patients; therefore, in an attempt to find new strategies and interventions aimed at reducing inflammation and consequently pain in OA, this study was designed to evaluate the anti-inflammatory effects of L-carnitine supplementation in females with knee OA.

MATERIALS AND METHODS

Subjects Selection

This randomized, double-blind, placebo-controlled trial was conducted between November 2013 and November 2014. The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (Iran) and registered on the Iranian Registry of Clinical Trials website (code: IRCT201311231197N17). All subjects were made aware of the content of the study and a written informed consent was obtained from each subject.

The sample size was calculated based on information obtained from studies by Farid et al. [32] and Geraci et al. [22] on the intensity of knee pain. Considering a confidence level of 95% and power of 80%, the sample was determined at least 30 cases in each group. The sample size was increased to 36 cases in each group for a possible dropout of 20%. Seventy-two volunteer women aged 40 to 60 years with the diagnosis of mild to moderate bilateral primary knee OA according to the American College of Rheumatology criteria [33, 34] and body mass index (BMI) of 25–34.9 kg/m^2 were recruited from the rheumatology clinics of Tabriz University of Medical Sciences. The exclusion criteria were as follows: BMI less than 25 or higher than 35 kg/m^2; secondary OA (due to a known disorder), synovitis, arthroscopy, surgery, or a joint injection of the target knee within the previous 6 months; history of knee joint replacement; 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; taking omega-3-fatty acids (e.g., fish oil) and antioxidant supplements; use of NSAIDs 2 weeks prior to and during the intervention. Because the use of NSAIDs was not allowed during the trial, patients were permitted to use acetaminophen for relieving pain and symptoms if it was necessary.

Study Design

The eligible participants were randomly allocated to intervention and placebo groups based on a random block procedure consisting of 4 subjects per block, which matched subjects to each block based on menopausal status, BMI, and age, produced by Random Allocation Software, version 1.0 (M. Saghaei, Department of Anesthesia, Isfahan University of Medical Sciences, Isfahan, Iran). A computer-generated random sequence was kept in a remote secure location and administered by an independent third party who was not involved with the clinical conduct of the study until all study data were collected and verified. Patients and those involved in enrolling participants, administering interventions, and assessing outcomes were blind to group assignments. The experimental group (n = 36) received 750 mg L-carnitine tartrate per day divided into 3 equal doses of one 250 mg tablet after each meal for 8 weeks (L-carnitine, Karen Pharmaceutical & Nutrilife Co., Yazd, Iran). The control group (n = 36) received placebo according to the same regimen and for the same duration (placebo, Karen Pharmaceutical & Nutrilife Co.). The placebo pills contained inactive ingredients with no therapeutic activity and an identical appearance. The participants were asked to maintain their usual dietary intakes and physical activity during the study period. Patients were monitored weekly for any side effects of L-carnitine supplementation.

At the onset of the study, all patients underwent routine physical examinations. Body weight was measured to the

nearest 0.1 kg using a Seca scale (Hamburg, Germany) and height was also measured using a mounted tape to the nearest 0.5 cm. BMI was calculated by dividing weight (in kilograms) by the square of height (in meters) [35]. Energy intake was calculated using a 24-hour recall method for 3 days (including 2 week days and 1 weekend day) a week before and at the end of supplementation by the Nutritionist IV software program (First Databank Inc., Hearst Corp., San Bruno, CA). A visual analog scale (VAS) assessment of pain was also included. With this assessment, a line of 100 mm is drawn to measure the individual's pain status, with 0 representing no pain and 100 being unbearable pain. Patients marked on this line the relevant amount of pain they were experiencing and the value was noted by the investigator, in millimeters [36]. Based on the distribution of pain VAS scores in patients who described their pain severity as none, mild, moderate, or severe, the following cut points on the pain VAS were recommended: no pain (0–4 mm), mild pain (5–44), moderate pain (45–74 mm), and severe pain (75–100 mm) [37].

At the beginning and at the end of the trial period, 5 mL of venous blood samples were collected after an overnight fast of 12 hours. The serum samples were separated from whole blood by centrifugation at 3200 rpm for 10 minutes and were kept at −80°C until biochemical analysis. Serum levels of high-sensitivity C-reactive protein (hs-CRP) were measured using an immunoturbidimetry method. Serum levels of IL-1β were measured using platinum enzyme-linked immunosorbent assay (ELISA) kits (Orgenium Laboratories, Vantaa, Finland). Serum levels of MMP-1 and MMP-13 were determined using human ELISA kits from Boster (Boster Biological Technology Co., Ltd., Pleasanton, CA). Using an ELISA plate reader (Model stat fax 2100, Awareness, Ramsey, MN) at a wavelength of 450 nm, the color changes were measured. All measurements were done following the instructions provided by the manufacturers.

Statistical Analysis

Statistical analysis was performed using SPSS version 16.0 software (SPSS, Inc., Chicago, IL). Normality of variables distribution was evaluated using the Kolmogorov-Smirnov test. Normally distributed variables were displayed as mean ± standard deviation and nonnormally distributed variables were presented as median (25th and 75th percentiles), respectively. The differences between variables before and after the intervention were compared by paired t test and or nonparametric Wilcoxon signed rank test. Between-group comparisons were made by independent sample t test and or nonparametric Mann-Whitney U test. Analysis of covariance (ANCOVA) was used to identify any differences between the 2 groups at the end of the study, adjusting for baseline values and covariates (duration of OA, changes in weight, and calorie intake). The sign and Mann-Whitney U tests were used for intra- and intergroup comparisons of the qualitative data, respectively. The percentage changes in variables within each group were determined by the following formula: [(after values − before values)/before values] × 100. A p value < 0.05 was considered statistically significant.

RESULTS

From 72 subjects who met the inclusion criteria and entered the study, 3 subjects in the L-carnitine group were withdrawn due to discontinuing intervention and lost to follow-up. Therefore, data were reported for 69 patients (33 in the L-carnitine group and 36 in the placebo group). In the L-carnitine group, the mean ± SD age and duration of OA were 51.63 ± 5.69 and 4.13 ± 3.83 and in the placebo group they were 52.44 ± 6.56 and 5.83 ± 5.92 years, respectively. No significant differences were observed in age and or duration of disease between the 2 study groups ($p > 0.05$). At baseline, the mean ± SD BMI and energy intake were 31.57 ± 3.06 kg/m^2 and 1883.27 ± 381.23 kcal/day in the L-carnitine group and 32.43 ± 3.16 kg/m^2 and 1845.64 ± 418.90 kcal/day in the placebo group, respectively. No significant differences were observed in anthropometric measures and daily energy intake between the 2 groups at baseline ($p > 0.05$). Anthropometric measures did not change significantly in either group after the supplementation period ($p > 0.05$). In comparison with baseline, total energy intake decreased significantly in the L-carnitine group by 7.88% ($p < 0.05$). At the end of the study, results of ANCOVA test did not show statistically significant differences between the 2 studied groups in anthropometric measures and total energy intake, adjusted for baseline values ($p > 0.05$).

Table 1 demonstrates serum biochemical parameters before and after intervention in the L-carnitine and placebo groups. No significant differences were observed between the 2 groups in terms of serum IL-1β, MMP-1, MMP-13, and hs-CRP levels at baseline ($p > 0.05$). Serum IL-1β levels decreased significantly in the L-carnitine group by 5.53% ($p < 0.05$), whereas it increased significantly by 5.51% in the placebo group ($p < 0.05$) after the experimental period (Table 1). Serum levels of MMP-1 decreased significantly in the L-carnitine group (median percentage of changes [25th and 75th percentiles], −19.10% [−46.05, 3.47], $p = 0.021$), whereas it did not change significantly in the placebo group (median percentage changes [25th and 75th percentiles], 15.20% [−17.83, 93.76], $p = 0.381$) after the supplementation period. Serum levels of MMP-13 (median percentage changes [25th and 75th percentiles], −7.28% [−46.31, 96.93], $p = 0.742$) and hs-CRP (median percentage changes [25th and 75th percentiles], −6.49% [−30.91, 35.08], $p = 0.505$) did not change significantly in the L-carnitine group after the study (Table 1). Moreover, no significant changes were observed in serum levels of MMP-13 (median percentage

Table 1. Comparison of Biochemical Variables in Treatment Groups before and after Intervention[a]

Variable	Measurement Period	L-Carnitine Group($n = 33$)	Placebo Group($n = 36$)	Mean Difference (95% CI)[b]	p Value[†]
IL-1β (pg/ml)	Baseline	9.82 ± 1.30	9.83 ± 1.80	−0.01 (−0.78, 0.76)	0.979
	After 8 weeks	9.20 ± 0.91	10.30 ± 1.56	−1.10 (−1.53, −0.68)	<0.001
	p Value[c]	0.001	0.011		
MMP-1 (pg/ml)	Baseline	379.0 (199.0, 707.75)	459.0 (219.0, 1239.0)	409.0 (219.0, 1049.0)	0.373
	After 8 weeks	296.5 (147.75, 681.5)	544 (304.0, 1325.25)	−0.18 (−0.31, −0.05)	0.006
	p Value[c]	0.021	0.381		
MMP-13 (pg/ml)	Baseline	80.0 (35.0, 130.0)	71.5 (37.0, 184.25)	74.0 (36.0, 173.0)	0.836
	After 8 weeks	79.0 (37.5, 126.0)	93.25 (44.75, 199.75)	−0.13 (−0.35, 0.07)	0.210
	p Value[c]	0.742	0.561		
hs-CRP (mg/L)	Baseline	2.79 (1.65, 5.38)	2.06 (1.16, 3.40)	2.37 (1.42, 3.93)	0.129
	After 8 weeks	2.49 (1.43, 3.98)	2.19 (1.52, 4.51)	−0.06 (−0.22, 0.09)	0.435
	p Value[c]	0.505	0.189		

CI = confidence interval, IL = interleukin, MMP = matrix metalloproteinase, hs-CRP = high-sensitivity C-reactive protein.

[a]Mean ± SD and median (25th and 75th percentiles) are presented for normally and nonnormally distributed measures, respectively. Medians of differences (25th and 75th percentiles) are presented for measures not normally distributed, instead of mean difference (95% CI).

[b]Independent sample t test and or Mann-Whitney U test for normally and nonnormally distributed measures, respectively, at baseline or ANCOVA test, adjusted for baseline values, changes in weight, calorie intake, and duration of osteoarthritis, after 8 weeks.

[c]Paired t test and or Wilcoxon signed rank test for normally and nonnormally distributed measures, respectively.

changes [25th and 75th percentiles], 12.90% [−38.06, 104.67], $p = 0.561$) and hs-CRP (median percentage changes [25th and 75th percentiles], 1.77% [−14.40, 50.67], $p = 0.189$) in the placebo group after the study (Table 1). At the end of the study, results of ANCOVA test showed statistically significant differences between the 2 groups only in serum IL-1β and MMP-1 levels ($p < 0.05$), adjusted for baseline values and covariates (Table 1).

As presented in Fig. 1A, at baseline according to VAS, 30.3% ($n = 10$), 57.6% ($n = 19$), and 12.1% ($n = 4$) of the participants in the L-carnitine group and 41.7% ($n = 15$), 41.7% ($n = 15$), and 16.7% ($n = 6$) of the participants in the placebo group had mild, moderate, and severe pain, respectively. At baseline, there were no significant differences in pain severity between the 2 study groups ($p > 0.05$). At the end of the study, significant differences in pain severity according to VAS were observed between the 2 groups ($p = 0.019$). Results of the sign test showed significant intragroup changes in pain severity in both the L-carnitine ($p < 0.001$) and placebo ($p = 0.012$) groups. Fig. 1B depicts the mean VAS score before and after intervention in the study groups. The differences in baseline scores were not statistically significant between the 2 study groups (mean difference [95% confidence interval (CI)], 0.49 [−0.51, 1.50], $p = 0.329$). After the supplementation, the mean VAS score decreased significantly by 52.67% in the L-carnitine group ($p < 0.001$) and by 21.82% in the placebo group ($p < 0.001$). At the end of the study, ANCOVA test revealed a significant difference between the 2 groups for mean VAS score (mean difference [95% CI], −12.84 [−20.95, −4.74], $p = 0.002$) adjusted for baseline values, changes in weight, calorie intake, and duration of OA.

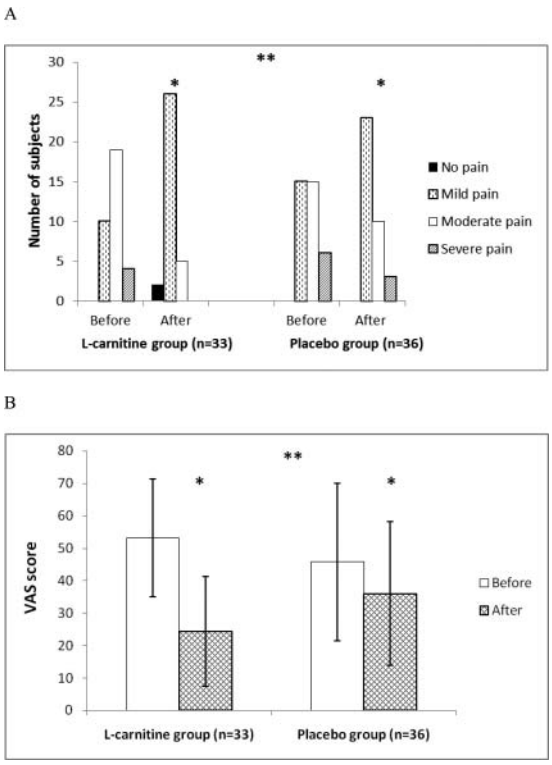

Fig. 1. (A) Number of subjects according to severity of pain VAS and (B) comparison of mean VAS score in treatment groups before and after intervention. (A) *Sign test for intragroup changes ($p < 0.001$ for the L-carnitine group and $p = 0.012$ for the placebo group). **Mann-Whitney U test for intergroup changes (at baseline: $p = 0.593$ and after 8 weeks: $p = 0.019$). (B) *Paired t test for intragroup changes ($p < 0.001$ for both L-carnitine and placebo groups). **Independent sample t test for intergroup changes at baseline ($p = 0.329$) and ANCOVA test adjusted for baseline values and covariates after 8 weeks ($p = 0.002$).

DISCUSSION

Taking into account the important role of inflammation in the pathogenesis of OA and the potential risks associated with long-term use of anti-inflammatory medications, today, many studies are focused on the development of new anti-inflammatory therapeutic approaches especially dietary supplementation. L-Carnitine is a dietary supplement that possesses anti-inflammatory effects and was recently reported to be effective in the management of arthritis [21, 22]. To the best of our knowledge, this is the first randomized clinical trial to assess the effects of L-carnitine supplementation on serum inflammatory factors in females with knee OA. Our results indicated that serum hs-CRP levels did not change significantly in the L-carnitine group compared to the baseline values and those in the placebo group (Table 1), which might be due to the disease stage, short duration of the study, or low dose of the supplement.

Unlike hs-CRP, which serves as an unspecific response to inflammation, one of the most well-studied cytokines involved in OA pathogenesis, IL-1β, has been shown to play an important role in both cartilage degradation and stimulation of nociceptive pathways [38–41]. Our results showed that L-carnitine supplementation led to significant reduction in serum levels of IL-1β compared to the baseline and those in the placebo group ($p < 0.001$). It has been reported that IL-1β stimulates the synthesis of other pro-inflammatory cytokines and proteolytic enzymes leading to the suppressed expression of essential extracellular matrix components (i.e., aggrecan and collagen type II) in chondrocytes, inhibiting extracellular matrix synthesis and promoting cartilage breakdown [42–44]. In addition, IL-1β has been shown to activate nociceptors directly through intracellular kinase activation and may also induce indirect nociceptive sensitization via the production of kinins and prostanoids [44]. Therefore, it seems that decreasing serum levels of IL-1β can be considered as a potential therapeutic approach to prevent cartilage degeneration and also improve clinical outcomes. The anti-inflammatory activity of L-carnitine has also been reported in previous studies using animal models [23–26] and human studies, including patients with type 2 diabetes mellitus [27], nonalcoholic steatohepatitis [28], and coronary artery disease [29] and patients undergoing hemodialysis [30, 31, 45] by lowering serum levels of inflammatory markers such as tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6, and hs-CRP.

Based on the literature reviews, there is no published article about the effects of L-carnitine supplementation on serum matrix metalloproteinases. Our results showed that L-carnitine supplementation led to significant reduction in serum levels of MMP-1 compared to the baseline and those in the placebo group (Table 1). Serum MMP-13 levels did not change significantly in the L-carnitine group compared to baseline and those in the placebo group (Table 1). It has been reported that IL-1β, a major cytokine involved in the physiopathology of OA, can stimulate chondrocytes to release several proteolytic enzymes, among which are MMP-1 and MMP-13 [46, 47]. These proteases are key regulators of cartilage destruction, making anti-cytokine therapy, especially that which targets IL-1β, an attractive strategy to counteract OA. Therefore, we could assume that reductions observed in serum MMPs levels are due to the decreased levels of serum IL-1β following L-carnitine supplementation. Supplementation with L-carnitine did not suppress serum MMP-13 levels significantly, which might be due to the short duration of the study or the low dose of the supplement.

Because inflammation is the main cause of pain in OA [48], supplementation with L-carnitine may have positive effects on pain by decreasing the inflammatory factors, which may lead to an improvement in physical function. Results of the present study indicated that the mean VAS score decreased significantly in the L-carnitine group compared to baseline and those in the placebo group (Fig. 1B). It has been reported that placebo could be effective in treatment of OA, especially for pain [49]. Because there were no significant differences between the 2 groups for acetaminophen use during the study (21.2% in the L-carnitine group and 22.2% in the placebo group, $p > 0.05$), the reduction in mean VAS scores in the placebo group is most likely due to the placebo effect. To the authors' knowledge, there was only one study investigating the effect of 12-week application of a food supplement sachet containing L-carnitine fumarate (345 mg) in combination with glucosamine sulfate, chondrotin sulfate, hydrolyzed collagen type II, and hyaluronic acid mixture in knee OA patients [22]. Our findings are consistent with Geraci et al. [22], who concluded that VAS score decreased significantly after the study ($p < 0.05$).

In general, the present findings should be interpreted considering the limitations of the study. First, the duration of the study was limited to only 8 weeks. Furthermore, the levels of inflammatory mediators and metalloproteinase enzymes were only measured in serum instead of the synovial fluids. Further studies with higher doses of L-carnitine, long-term supplementation, and measuring other inflammatory and anti-inflammatory mediators such as TNF-α, IL-6, IL-10, and MMP-3 are warranted. The strengths of our study were weekly monitoring of patients by phone call and high acceptance of L-carnitine in patients.

CONCLUSION

In conclusion, despite observed beneficial effects of short-term supplementation of L-carnitine in decreasing serum inflammatory mediators, especially IL-1β and MMP-1, and improving pain in knee OA patients, further studies are needed to achieve concise conclusions.

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