Effects of L-carnitine supplementation on the quality of life in diabetic patients with muscle cramps

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Abstract. Diabetic patients often suffer from muscle cramps. This study aimed to compare the quality of life (QOL) of diabetic patients with and without muscle cramps and to investigate the effect of L-carnitine supplementation in diabetic patients with muscle cramps. A total of 91 patients with diabetes were enrolled in this study: 69 patients with muscle cramps and 22 patients without muscle cramps. Muscle cramps and QOL were evaluated using the muscle cramp questionnaire and the Short Form 36 health survey version 2 (SF-36), respectively. Clinical characteristics were compared between diabetic patients with and without muscle cramps. In the prospective portion of the study, 25 diabetic patients with muscle cramps received L-carnitine supplementation (600 mg/day orally) for 4 months. The questionnaires were administered before and after supplementation. The SF-36 scores in diabetic patients with muscle cramps were lower than those in patients without muscle cramps on the subscales of physical function, role physical, bodily pain, vitality, general health, and social function. In the 25 patients with muscle cramps who received L-carnitine supplementation, the monthly frequency of muscle cramps and Wong-Baker FACES® Pain Rating Scale scores were significantly decreased. Scores on the following SF-36 subscales improved after L-carnitine supplementation: body pain, vitality, social function, and role emotional. This study demonstrated that muscle cramps decrease the QOL in patients with diabetes, and L-carnitine supplementation may improve the QOL by reducing the frequency and severity of muscle cramps in these patients.

Key words: Quality of life, Levocarnitine, Muscle cramp, Diabetes mellitus

MUSCLE CRAMPS are a common symptom of painful contractions of a muscle group and are sometimes disabling [1]. Certain physical activities and medical conditions, such as exercise, hepatic and renal dysfunction, and polyneuropathy due to neurological conditions or diabetes mellitus, can cause muscle cramps [1]. Muscle cramps commonly occur in patients with cirrhosis and those undergoing hemodialysis [2, 3]. Some reports indicate that approximately 60% of patients with diabetes have experienced muscle cramps and that the pain they experience is more severe than that experienced by healthy people [1, 4]. Muscle cramps are thus speculated to impair QOL in patients with diabetes.

The Short Form 36 Health Survey version 2 (SF-36) is a tool for evaluation of QOL and has been commonly used in large population studies and clinical studies [5, 6]. In the Australian Diabetes, Obesity and Lifestyle Study, which was a population-based study of around 11,000 people, the SF-36 score in patients previously diagnosed with diabetes was significantly lower than that in individuals with normal glucose tolerance [7]. In a Malaysian study, type 2 diabetes mellitus patients with glycosylated hemoglobin (HbA1c) levels >7.5% (indicating poor glycemic control) had lower SF-36 scores than those with HbA1c levels ≤7.5% [8]. The SF-36, a short self-administered questionnaire used to assess general health status, has been cross-culturally adapted for use in Japanese patients, and has a high degree of acceptability and data quality [9, 10]. The Japanese version of the SF-36 was translated, adapted, and validated from the American English version by Fukuhara et al., whose results confirmed the reliability and equivalence of both the Japanese and American versions [9, 10].

Muscle cramps are often self-limiting and can usually be managed without professional medical treatment;
however, pharmacotherapy may be needed when the symptoms are persistent and disabling. Commonly used medications for the treatment of muscle cramps include B-complex vitamins, diltiazem, carbamazepine, mexiletine, and Shakuyaku-kanzo-to [1].

A recent study revealed that L-carnitine supplementation reduces muscle cramps in patients undergoing hemodialysis [3]. L-carnitine has also been shown to alleviate muscle weakness and aches, and decrease the visual analog pain scale score in patients with cirrhosis [2]. Carnitine is associated with the import of long-chain fatty acids into mitochondria for β-oxidation, which is the major source of energy for cardiac and skeletal muscle cells [11]. Previous reports revealed that the mean free L-carnitine level in the serum of diabetic patients with complications was lower than that in patients without complications [12]. In another report, L-carnitine levels were significantly lower in patients with neuropathic pain, especially when it was caused by diabetes [13].

In this study, we compared the clinical and patient characteristics of diabetic patients with and without muscle cramps. We also investigated the clinical effects of L-carnitine on muscle cramps and QOL in patients with diabetes.

**Materials and Methods**

**Study design and participants**

A total of 91 patients with diabetes who visited the outpatient clinic of the Department of Diabetes, Metabolism, and Endocrinology at Osaka Medical College Hospital were enrolled in this study. Diabetes was diagnosed on the basis of the criteria proposed by the Japan Diabetes Society. All patients were treated with oral hypoglycemic agents and/or insulin for type 1 or type 2 diabetes.

A total of 69 patients reported experiencing muscle cramps. Of these 69 patients, 25 who wished to receive L-carnitine supplementation were enrolled in the prospective portion of this study. In the prospective study, 300 mg levocarnitine chloride (L-carnitine tablets, Otsuka Pharmaceutical Co., Ltd, Japan) was prescribed to these patients twice a day (total dose of 600 mg/day) for 4 months. Four patients dropped out for economic reasons. Thus, 21 patients received L-carnitine supplementation for the entire 4 months. Before and after 4 months of L-carnitine supplementation, the cramp questionnaire and SF-36 were re-administered to these participants (Fig. 1). The diabetes treatment received by these patients could be changed to achieve better glycemic control at any time during the study.

In the group of L-carnitine supplementation, three had already started receiving treatment for muscle cramps (one treated with Shakuyaku-kanozo-to, two treated with pregabalin) before the enrollment, and the treatment continued without change in dose throughout the study.

**Patient assessments**

All subjects completed the cramp questionnaire and the SF-36 questionnaire. The cramp questionnaire was a slightly modified version of a previously published questionnaire, and included a description of the frequency and severity of pain caused by muscle cramps according

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Fig. 1  The algorithm followed for inclusion in this current study.
to Wong-Baker FACES® Pain Rating Scale that ranged from 0 (no hurt) to 5 (hurts worst) [14]. The Wong-Baker FACES® Pain Rating Scale was originally published in Whaley & Wong’s Nursing Care of Infants and Children. QOL was assessed using the Japanese version of the SF-36 [6]. The SF-36 comprises eight subscales: physical function (PF), role physical (RP), bodily pain (BP), vitality (VT), general health (GH), role emotional (RE), social function (SF), and mental health (MH). The score on each subscale ranges from 0 to 100 points, with higher scores indicating a better QOL.

Blood samples were collected before and 4 months after L-carnitine supplementation to measure the levels of random blood glucose, HbA1c, and serum creatinine. Blood glucose and HbA1c levels were measured using hexokinase enzymatic analysis and high-performance liquid chromatography, respectively.

Information on the other variables, of physical parameters (height and body weight) and complications, was extracted from the patients’ medical records. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m²).

Statistical analyses
All data were statistically analyzed using SPSS software, version 22 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean and standard deviation, or range and median. The Mann–Whitney U test was used for statistical analysis of patient characteristics and scores on the SF-36 subscales. The Wilcoxon signed rank test was used to compare parameters before and after L-carnitine supplementation.

Compliance with ethical standards
All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Osaka Medical College (No. 1256) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants in the study were provided clear information about the study and provided written informed consent.

Results
QOL of diabetic patients suffering muscle cramps
As shown in Table 1, there were no differences in age, BMI, and HbA1c, blood glucose, and creatinine levels between the participants with and without muscle cramps. Table 2 shows that the scores in participants with muscle cramps were significantly lower than those in the participants without muscle cramps on the subscales of PF, RP, BP, VT, GH, and SF.

Table 1 Clinical characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Muscle cramp (+)</th>
<th>Muscle cramp (–)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (Male/Female)</td>
<td>69 (31/38)</td>
<td>22 (11/11)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 ± 11</td>
<td>60 ± 16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 5.3</td>
<td>26.2 ± 4.7</td>
</tr>
<tr>
<td>Type of diabetes (type 1/type 2)</td>
<td>5/64</td>
<td>0/22</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>180.7 ± 81.8</td>
<td>160.3 ± 59.5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.4 ± 2.9</td>
<td>9.5 ± 1.8</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.86 ± 0.68</td>
<td>0.73 ± 0.23</td>
</tr>
<tr>
<td>Frequency of muscle cramps per month</td>
<td>6.7 (0.1–150.0)†</td>
<td>0</td>
</tr>
<tr>
<td>Visual analogue scale for pain</td>
<td>3.8 (0–5)†</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are means ± standard deviation, median (min-max) or numbers of participants. † indicates p < 0.05 compared to the value for the group with muscle cramps, calculated by Mann-Whitney test.

Table 2 Participant scores on the SF-36 subscale

<table>
<thead>
<tr>
<th></th>
<th>Muscle cramp (+)</th>
<th>Muscle cramp (–)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>72.0 ± 18.2†</td>
<td>84.3 ± 17.1</td>
</tr>
<tr>
<td>Role Physical</td>
<td>67.0 ± 26.3†</td>
<td>83.2 ± 24.8</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>51.2 ± 24.7†</td>
<td>78.5 ± 22.4</td>
</tr>
<tr>
<td>General Health</td>
<td>43.3 ± 17.1†</td>
<td>50.5 ± 13.7</td>
</tr>
<tr>
<td>Vitality</td>
<td>48.7 ± 21.5†</td>
<td>64.5 ± 18.3</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>70.3 ± 24.3†</td>
<td>85.8 ± 19.8</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>70.5 ± 26.2</td>
<td>80.3 ± 27.2</td>
</tr>
<tr>
<td>Mental Health</td>
<td>62.0 ± 21.1</td>
<td>65.5 ± 18.0</td>
</tr>
</tbody>
</table>

Values are means ± standard deviation. † indicates p < 0.05 compared to the value for the group with muscle cramps, calculated by Mann-Whitney test.

Impacts of insulin treatment and complications on QOL
As shown in Table 3, no statistically significant differences were observed in all SF-36 subscale scores between the diabetic patients treated with and without insulin or those with and without diabetic nephropathy. The scores on PF, RP and RE were significantly lower in diabetic patients with diabetic retinopathy.
QOL by L-carnitine supplementation

Table 4 shows that both the frequency of muscle cramps per month and score of Wong-Baker FACES® Pain Rating scale decreased significantly 4 months after L-carnitine supplementation. It also resulted in a significant increase in blood glucose levels; but no significant changes in HbA1c and creatinine levels. Fig. 2 shows that the scores on the BP, VT, SF, and RE subscales of the SF-36 were significantly higher 4 months after L-carnitine supplementation compared to those before the supplementation.

Discussion

In the current study, 69 of the 91 patients with diabetes (75%) complained of muscle cramps and the scores of diabetic patients with muscle cramps on the SF-36 subscales of PF, RP, BP, GH, VT, and SF were significantly lower than the scores of diabetic patients without muscle cramps. We also revealed that L-carnitine supplementation resulted in a decrease in the frequency of muscle cramps and in the score of Wong-Baker FACES® Pain Rating scale, and an increase in SF-36 scores.

Our study revealed that percentage of suffering muscle cramps in the diabetic patients is similar to the previous report that the prevalence rates of muscle cramps are 39.5%, 57.5%, and 75.5% in healthy individuals, and patients with type 1 and type 2 diabetes, respectively [4]. Diabetic patients who experienced muscle cramps had impaired QOL according to our study. The scores of diabetic patients with muscle cramps on the SF-36 subscales of PF, RP, BP, GH, VT, and SF were significantly lower than the scores of diabetic patients without muscle cramps. The decrease in these scores reflects a decrease in the QOL of these patients as shown in previous studies. Painful diabetic neuropathy has a considerable impact on patients’ QOL because of the consequent sleep loss and reduction in energy levels [5, 15]. Cocito and colleagues revealed that pain worsened the QOL in patients with neuropathy [16]. Other studies revealed that scores of patients with painful diabetic polyneuropathy on all eight SF-36 subscales were lower than the scores of patients with non-painful diabetic polyneuropathy [17, 18].
The scores on SF-36 subscale of PF, RP and RE were significantly lower in diabetic patients with diabetic retinopathy. Previous reports showed visual impairment due to diabetic retinopathy has a significant negative impact on patients’ quality of life [19]. Our results possibly indicate that participants with diabetic retinopathy had lower QOL in addition to those with muscle cramps.

To the best of our knowledge, this is the first report of L-carnitine supplementation improving the symptoms and QOL in diabetic patients with muscle cramps. L-carnitine supplementation resulted in a decrease in the frequency of muscle cramps and in Wong-Baker FACES® Pain Rating Scale score, and associated with an increase in the scores on the BP, VT, SF, and RE subscales of the SF-36. Several previous studies have also shown that L-carnitine supplementation is commonly utilized in patients with inborn errors of carnitine metabolism and muscular carnitine deficiency [11], hemodialysis patients with muscular symptoms [3], and cirrhosis patients who experience muscle cramps [14].

In another point of view, relief from pain caused by muscle cramps mainly improved the mental health of QOL. We have already mentioned before that the SF-36 comprises eight subscales. In the original American English version, the four subscale (PF, RP, BP and GH) measures are often given the greatest weights to form a “physical component” [20]. The other four subscales (VT, SF, RE, and MH) are the greatest contributors to a “mental component” [20]. These two components are conceived as being parts of a higher-order concept of QOL than the eight subscales [21]. In this study, the SF-36 subscales of PF, RP, BP and GH in physical component and VT and SF in the mental component were significantly lower in patients with painful muscle cramps. L-carnitine supplementation was associated with the relief of pain and with an increase in the scores only on the BP in the physical component but the scores in 3 of 4 mental component subscales, VT, RE, and SF, of the SF-36. These findings suggest that the relief of pain from muscle cramps was mainly psychological. The report from Cocito and colleagues also revealed that the mental composite score correlated only with pain and not with the presence of neuropathy [16]. A study by Sabatowski et al. revealed that pregabalin treatment of post-herpetic neuralgia significantly improved pain and the scores on the BP, VT, and MH subscales of the SF-36 [22].

Our study has some limitations. First, this was a single center study. Second, patient allocation was not randomized or double-blinded because the attending physician prescribed L-carnitine supplementation according to the patients’ wishes. The current study did not have a control group, and it is difficult to disprove a placebo effect. Third, the sample size was small and four participants dropped out because they could not financially afford the L-carnitine supplementation. More studies, such as interventional trials with a larger sample size, are needed to
confirm the current these findings.

In conclusion, our findings indicate muscle cramps decrease the QOL in patients with diabetes, and that L-carnitine supplementation alleviates muscle cramps and improves the QOL in diabetic patients with muscle cramps. Thus, clinicians should consider L-carnitine sup-

plementation in diabetic patients with muscle cramps.

**Disclosure**

None of the authors have any potential conflicts of interest associated with this research.

**References**