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Effect of L-carnitine on diabetic neuropathy and ventricular dispersion in patients with diabetes mellitus

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Aim: Diabetes is a common cause of polyneuropathy. Cardiac arrhythmias and markedly increased mortality rate have been demonstrated in patients with diabetic neuropathy and also demonstrated that abnormally prolonged QT dispersion interval (QTd) is associated with a higher risk of ventricular arrhythmias and sudden death. We investigated the efficacy and tolerability of L-carnitine (LC) in the treatment of diabetic neuropathy and ventricular dispersion, mainly by evaluating the effects of treatment on electrophysiological parameters.

Materials and methods: We recruited 30 patients with type I or type II diabetes (mean age: 60 ± 9 years, range: 36-75; 18 males, 12 females) meeting clinical and neurophysiological criteria for diabetic neuropathy. All of the patients were given LC 2 g/day for 10 months. Blood glucose regulation was maintained by diet, oral antidiabetic, or insulin. To determine the nerve functions electrophysiologically, superficial electrode distal latency, amplitude, nerve conduction velocity in median and ulnar nerves in the upper extremities and peroneal, tibial and sural nerves in the lower extremities and F response in motor nerves were studied. Resting 12-lead electrocardiograms were recorded for measurements of QTd, corrected QTd (QTcd), JT dispersion (JTd), and corrected JT dispersion (JTcd).

Results: After 10 months of treatment, median, ulnar, and tibial nerves' motor nerve conduction velocities ($P < 0.05$) and M-wave amplitudes ($P < 0.05$) increased; distal latencies and the F-wave latencies ($P < 0.05$) decreased; ulnar, sural, and median sensory nerve action potential amplitude ($P<0.01$) and nerve conduction velocities ($P < 0.05$) increased; distal latencies ($P < 0.05$) decreased; and , QTd, QTcd, JTd, and JTcd ($P < 0.05$) decreased significantly when compared to basal values. The greatest changes in sensory nerve action potential amplitude and ventricular dispersion parameters were observed in the sensory sural nerve and QTcd, respectively. LC was well tolerated over the study period.

Conclusion: LC, well tolerated by diabetic patients, may improve peripheral neuropathy and ventricular dispersion and may be useful in preventing the increased incidence of arrhythmias and sudden death observed in such patients. Larger clinical trials are needed to confirm these data before changes to clinical practice can be advocated.

Key words: L-carnitine, diabetic polyneuropathy, electromyography, ventricular dispersion

Diabetik polinöropatili hastalarda ventriküler dispersiyon üzerine karnitinin etkinliği

Amaç: Diyabet en yaygın polinöropati sebebidir. Diabetik polinöropatili hastalarda kardiyak ritim ve ventriküler dispersiyon bozukluklarının ani ölümlere sebep olduğu ve mortaliteyi artırdığı gösterilmiştir. Bu çalışmada, diabetik polinöropatili hastalarda karnitinin ventriküler dispersiyon parametreleri ve nöropati üzerine etkinliğini ve yan etkilerini araştırdık.

Yöntem ve gereç: Çalışmamıza polinöropatili 30 (18 erkek, 12 kadın) diabetik hasta alındı. Hastalara 10 ay boyunca 2 gr/gün karnitin uygulandı. Tedavi öncesi ve sonrası olguların hepsinde üst ekstremitelerde median ve ulnar, alt ekstremitelerde peroneal, tibial ve sural sinirlerde distal latans, amplitüd, sinir ileti hızı, motor sinirlerde F yanıtı çalışıldı. Ayrıca 50 mm/sn hızında 2 mV amplitüdünde standart 12 derivasyon elektrokardiyografi (EKG) çekimleri yapıldı. Ortalama QT, JT, QTc, JTc, RR intervali, QT, JT, QTc, JTc dispersiyonu (d) saptandı.

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Bulgular: İncelenen tüm sinirlerde ileti parametrelerinin hepsinde iyileşme gözlendi. Bazal değerlerle karşılaştırıldığında median, ulnar ve tibial sinirlerin motor ileti hızları ($P < 0,05$) ve bileşik kas aksiyon potansiyelleri ($P < 0,05$) anlamlı olarak artmış; distal latans ve F-cevabı latansları ($P < 0,05$) düşmüştü; ulnar, sural ve median sensoriyal ileti hızı amplitutleri ($P<0,01$) ve ileti hzları ($P < 0,05$) anlamlı olarak artmış; distal latansları ($P < 0,05$) düşmüştü. QTd, QTcd, JTd, ve JTcd ($P < 0,05$) anlamlı olarak düşmüştü. En belirgin düzelme sural sinir sensorial aksiyon potansiyelinde ve QTcd gözlendi. Karnitin çalışma periyodunca iyi tölere edildi.

Sonuç: Karnitin tedavisi ciddi bir yan etki olmaksızın ventriküler dispersiyon ve elektrofizyolojik değerlerde belirgin düzelme sağlamıştır. Ancak, ilacın etkinliği ve güvenilirliği açısından daha uzun süreli ve geniş skalalı çalışmalara gereksinim vardır.

Anahtar sözcükler: Diabetik nöropati, L-karnitin, elektromyografi, ventriküler dispersiyon

Introduction

A common complication of diabetes mellitus is peripheral neuropathy that can affect both somatic (1) and autonomic nervous systems (2), and the pathophysiological characteristics of diabetic neuropathy are complicated. A variety of hypotheses, including biochemical and vascular factors attributable to the reversible metabolic consequences of hyperglycemia, insulin deficiency, or both for the pathogenesis of this complication, have been proposed (3-5). Hyperglycemia is proposed to promote oxidative stress and generate reactive oxygen species (ROS), leading to inhibit mitochondrial respiratory enzymes and promote neuronal apoptosis (6,7). Insulin deficiency can promote alterations in fatty acid metabolism via blockade of the conversion of linoleic acid to linolenic acid (8), perturbing the production of vasodilating eicosanoids (9,10). Also, the accumulation of long-chain fatty acid esters disturbs cellular metabolism and membrane functions (11).

Carnitine and its short-chain esters facilitate transport of long-chain fatty acids across the inner mitochondrial membrane for β-oxidation, thereby promoting energy availability and preventing toxic accumulation of long-chain fatty acids (12). Furthermore, carnitine deficiency in diabetic tissues has received considerable attention concerning its role in the pathogenesis of diabetic neuropathy (13,14). Nakamura et al. (15) also reported that there was a close relationship between increased polyol pathway activity and carnitine deficiency in the development of diabetic neuropathy, and that an aldose reductase inhibitor and LC have therapeutic potential for the treatment of diabetic neuropathy. Carnitine uptake into cells is partially dependent on Na^+/K^+-ATPase (16). It is well known that decreased Na^+/K^+-ATPase activity in nerves can be ameliorated by treatment with aldose reductase inhibitors in diabetic rats (17).

A prolonged QT interval, as measured with a standard electrocardiogram (ECG), is associated with an increased risk of arrhythmias and sudden death (18). In addition, QTd appears to be a better prognostic marker than maximum QT interval, particularly in patients without previous cardiac diseases (19). Wheeler et al. (20) reported that diabetic patients with autonomic neuropathy have decreased the heart rate variability. Moreover, the autonomic nervous system effects the QT interval and QT prolongation observed in diabetic patients with autonomic dysfunction (21). The effect of LC on the increased QTd has never been studied. We investigated the efficacy of LC in the treatment of diabetic neuropathy and increased ventricular dispersion.

Material and methods

We recruited 30 patients with type I or type II diabetes (mean age: 60 ± 9 years, range: 36-75 years; 18 males, 12 females) meeting clinical and neurophysiological criteria for diabetic neuropathy. The demographic characteristics of patients are presented in Table 1. All of the patients were given LC 2 g/day for 10 months. Blood glucose regulation was maintained by diet, oral antidiabetic, or insulin. There was no other systemic or neurological disorder that can lead to peripheral neuropathy except diabetes

mellitus in these cases and all of them were examined 10 months before and after the treatment. Changes in the neuropathy symptom and deficit, electrophysiological peripheral-nerve conduction studies, and the ventricular dispersion parameters were assessed at the end of 10 months. To determine the nerve functions electrophysiologically, superficial electrode motor distal latency, amplitude, nerve conduction velocity and F response in median, ulnar, peroneal, tibial nerves and orthodromic sensory distal latency, amplitude, and nerve conduction velocity in median, ulnar, sural nerves were studied in both upper and lower limbs using conventional techniques. Resting 12-lead electrocardiograms were recorded with paper speed of 50 mm per second and standardizations of 0.5 mV per centimeter for measurement of QTd, corrected QTd (QTcd), JT dispersion (JTd), and corrected JT dispersion (JTcd). The QT and JT intervals were measured from beginning and from the end of the QRS complex, respectively, to the end of T. If U waves were present, QT interval was measured to the nadir of the curve between the T and U waves. None of the patients was taking any antiarrhythmics or drugs that may alter the results of QT and JT analysis. In the analyses of the QT and JT intervals, the values of the maximum QT and JT interval were used and Bazett's formula (QTc=QT / RR) was applied for heart rate correction (QTc, JTc). The QT and JT dispersion were defined as the difference between the maximum and the minimum QT and JT intervals, respectively, in any of the 12 leads. The study complies with the Declaration of Helsinki II and the study protocol was approved by the local ethics committee. Written informed consent was obtained from each participant. Data are expressed as mean ± standard deviation and were computed with SPSS. Wilcoxon Signed Ranks test was used to compare before and after treatment values. Results were considered to be statistically and significantly different when confidence limits exceeded 95% ($P < 0.05$).

Results

One patient was excluded from the study because he did not come for follow-up after treatment. At the end of the first month, all symptoms associated with neuropathy improved in all cases. After 10 months of treatment, median, ulnar, and tibial motor nerve conduction velocities ($P < 0.05$) and M-wave amplitudes ($P < 0.01$) increased, and distal latencies and the F-wave latencies ($P < 0.05$) decreased; ulnar, sural, and median sensory nerve action potential amplitudes ($P < 0.01$), and nerve conduction velocities ($P < 0.05$) increased, and distal latencies ($P < 0.05$) decreased (Table 2); QTd, QTcd, JTd, and JTcd ($P < 0.05$) decreased (Table 3) significantly compared to the values obtained before treatment. The greatest changes in sensory nerve action potential amplitude and QT parameters were observed in the sensory sural nerve and QTcd, respectively (Table 1-2). LC was well tolerated over the study period. Of 30 patients, 2 (6.6%) experienced excessive sweating and 3 (10%) had the symptoms of gastrointestinal system but none of the patients stopped treatment due to side effects.

Table 1. The demographic characteristics of diabetic patients.

Number of total patients	30
Female gender, N (%)	18 (60)
Male age, years	49.92 ± 10.66
Female age, years	53.26 ± 8.08
Duration of diabetes, years	12.8 ± 6.15 (1-30)
Use of insulin	43.3%
Use of oral antidiabetic	56.7%
Number of patients with carpal tunnel syndrome	73.3%

Table 2. Mean values and comparison between values of some electrophysiological parameters before and after treatment.

		Before treatment	After treatment
Right median motor	distal latency (msec)	4.35 ± 0.8	4.2 ± 0.6*
	amplitude (mV)	6.82 ± 2.6	8.27 ± 2.6**
	NCV (m/sec)	49.9 ± 9.3	56.3 ± 7.3*
	F response latency (msec)	30.5 ± 7.1	28.5 ± 2.4*
Right ulnar motor	distal latency	3.09 ± 0.47	2.72 ± 0.5*
	amplitude	8.32 ± 2.15	9.69 ± 1.7**
	NCV	52.1 ± 6.1	55.1 ± 11*
	F response latency	28.7 ± 2.6	27.3 ± 2*
Right peroneal motor	distal latency	5.0 ± 0.7	4.3 ± 0.4*
	amplitude	2.8 ± 1.5	3.2 ± 1.7**
	NCV	39.8 ± 4.4	40.2 ± 4.6
	F response latency	53.0 ± 6.7	55.3 ± 4.7
Right tibial motor	distal latency	5.2 ± 0.7	4.7 ± 0.6
	amplitude	3.7 ± 1.9	5.8 ± 2.4**
	NCV	37.6 ± 4.4	39.6 ± 3.7*
	F response latency	55.4 ± 6.1	52.8 ± 5.3*
Left peroneal motor	distal latency	4.9 ± 0.5	4.4 ± 0.8
	amplitude	3.0 ± 1.6	3.2 ± 1.4
	NCV	40.8 ± 5.8	39.8 ± 3.4
	F response latency	48.3 ± 12.6	51.6 ± 8.7
Left tibial motor	distal latency	5.5 ± 0.9	4.7 ± 0.8*
	amplitude	3.9 ± 2.2	6.7 ± 3.3**
	NCV	38.7 ± 6.3	42.8 ± 4.2*
	F response latency	56.7 ± 4.0	52.9 ± 6.7
Right median sensory a	NCV	32.0 ± 6.1	36.8 ± 4.4*
Right ulnar sensory	NCV	36.3 ± 3.0	38.6 ± 3.5*
Right sural sensory	Amplitude (μV)	4.7 ± 2.8	7.0 ± 7.5**
	NCV	29.3 ± 4.3	34.9 ± 6.5*
Left sural sensory	amplitude (μV)	5.6 ± 3.5	9.1 ± 5.8**
	NCV	28.5 ± 5.2	32.0 ± 4.3*

NCV: Nerve conduction velocity; *P < 0.05, **P < 0.01, all in comparison to base line values

Table 3. Mean values and comparison between values of ventricular dispersion parameters before and after treatment (*P < 0.05).

	Before treatment	After treatment
QT (ms)	341 ± 35	375 ± 22
JT (ms)	282 ± 35	296 ± 27
QTc (ms)	12 ± 0.63	13 ± 0.84
JTc (ms)	10 ± 0.81	11 ± 0.72
QT-d (ms)	81 ± 33	35 ± 11*
JT-d (ms)	65 ± 22	26 ± 11*
QTc-d (ms)	3 ± 1.3	1 ± 0.35*
JTc-d (ms)	2.7 ± 1.2	0.94 ± 0.33*
RR (ms)	762 ± 141	813 ± 127

Discussion

As yet, there is no effective treatment to prevent the development or progression of human diabetic neuropathy. Therapeutic interventions that have been tried include optimal glycemic control (22), aldose-reductase inhibitors (23), gamma linoleic acid (24), and antioxidants (25). It has been believed that the plasma carnitine level is an indicator for energy metabolism of the cell. Carnitine deficiency causes a defect in energy metabolism and decreases energy production. Moreover, carnitine deficiency in diabetic tissues has received considerable attention concerning its role in the pathogenesis of diabetic neuropathy (13,14). In a previous study, it has been suggested that experimental diabetic neuropathy is associated with depletion of LC in peripheral nerve (26), which may further limit mitochondrial fatty acid transport and oxidation (12), and it has also been reported that treatment with carnitine analogs can improve diabetic neuropathy and prevent the delay in motor nerve conduction velocity and electrophysiological abnormalities (13,14,26-28). We found that LC improved diabetic neuropathy and prevented the delay in motor nerve conduction velocity and other electrophysiological abnormalities similar to the results of the previous studies (13,14,26-28).

In addition, LC improves nerve regeneration after crush injury (29), neuromuscular dysfunction in normal rats (30), various abnormalities in cardiac function and biochemistry after ischemia or reperfusion (31), HIV-associated antiretroviral toxic neuropathy (32), and chemotherapy-induced neuropathy after cisplatin or paclitaxel treatment without showing any interference with the antitumor activity of the drugs (33). However, the effect of LC on the increased QTd has never been studied before. A prolonged QT interval, as measured with a standard electrocardiogram (ECG), is associated with an increased risk of arrhythmias and sudden death (18). Diabetic patients have increased QTd compared to non-diabetics even those without arterial hypertension and cardiovascular complications and with recent diagnosis (34). Furthermore, a prolonged QTd has been shown to be a strong and independent predictor of cardiac mortality in diabetes mellitus (DM) (35), and it has been reported that QT interval parameters give additional prognostic information in patients with DM, beyond that obtained from traditional risk factors (19). Recently, it has been shown that l-carnitine is able to increase hair shaft elongation and prolong anagen by upregulation of proliferation and downregulation of apoptosis in organ-cultured human scalp hair follicles (36). In this study, we found that the efficacy of LC in the treatment of increased QTd in patients with DM was significant when compared to the baseline values.

Hyperglycemia-driven mitochondrial over-production of ROS has recently been identified as the underlying biochemical abnormality in diabetic complications (37). LC would decrease the Ca^{++} concentration by improving Na^{+}/K^{+}-ATPase activity, as previously reported (38). The efficacy of LC in the treatment of increased QTd in patients with DM may be due to the restored myocardial ischemia. Hyperglycemia-induced ROS production in mitochondria not only occurs in endothelial cells but also in platelets. The result of increased ROS production of platelets is, among others, increased aggregation and an increased release of cytokines (39). Carnitine protects the cell membrane and DNA against the damage induced by free oxygen radicals. It prevents protein oxidation and pyruvate and lactate oxidative damage (40,41). Our results are in accordance with the results of the previous studies.

In conclusion, LC may improve peripheral neuropathy and ventricular dispersion and is well

tolerated in patients with diabetes, which may be useful in preventing the increased incidence of arrhythmias and sudden death observed in such patients. The beneficial effects of LC on the progression of neuropathy and risk for cardiovascular event must be studied in large, randomized, and controlled trials before changes in clinical practice can be advocated.

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