Interfascicular Gliding Dysfunction Relation with Focal Neuropathy in Diabetic Patients with Carpal Tunnel Syndrome

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J Hand Microsurg 2022;14:3–9.

Abstract

Carpal tunnel syndrome (CTS), a common neuropathy of the upper limb, is highly prevalent in diabetic patients. Recent findings indicate that changes in median nerve elasticity and its gliding characteristics may contribute to the development of CTS. Normally, each nerve should be able to adapt to the positional changes by passive movement relative to the surrounding tissues. This ability is provided by a gliding apparatus around the nerve trunk in the surrounding soft tissue. The fascicles of nerve trunks can also glide against each other (interfascicular gliding). Sonoelastography indicates that nerve elasticity is decreased in patients with CTS compared to healthy patients. Moreover, decreased nerve elasticity in diabetes mellitus type II is associated with increased neuropathy, especially in peripheral nerves. Biomechanical factors, oxidative stress, and microvascular defects are also observed in diabetic neuropathy and account for different complications. A reduction in the elasticity of peripheral nerves may be related to decreased interfascicular gliding because of the biomechanical changes that occur in neuropathy. Surgical treatments, including nerve release and reduction of carpal tunnel pressure, improve peripheral gliding but do not resolve disease symptoms completely. According to the evidence, interfascicular gliding dysfunction is the most important factor in the pathogenesis of CTS in diabetic patients. Available evidence suggests that biomechanical variations affect interfascicular gliding more than peripheral gliding in diabetic patients. Decreased nerve elasticity is strongly correlated with decreased interfascicular gliding. It is further hypothesized that the concurrent use of antioxidants and pharmacological treatment (neuroprotection) such as alpha lipoic acid with carpal tunnel release in diabetic patients may alleviate the interfascicular gliding dysfunction and improve median neve elasticity. Decreased nerve elasticity and interfascicular gliding dysfunction play significant roles in the pathogenesis of CTS in diabetic patients.

Keywords
- focal diabetic neuropathy
- nerve elasticity
- carpal tunnel syndrome

Introduction

Carpal tunnel syndrome (CTS) is a common disease of the upper limbs in patients with diabetes.[1] High CTS prevalence (~30%) has been reported in patients with diabetes and peripheral polyneuropathy. However, the syndrome was present in only 14% of patients with diabetes without late complications.[1,2] The duration of diabetes is an important risk factor for CTS.[3] Although the exact etiology of CTS is unknown, it is generally associated with special conditions such as obesity, arthritis, hypothyroidism, diabetes mellitus, trauma, mass lesions, amyloidosis, and sarcoidosis.[4] Treatment of CTS is less successful in patients with diabetes who concomitantly

published online
October 4, 2020

DOI https://doi.org/10.1055/s-0040-1718236
ISSN 0974-3227.

suffer from polyneuropathy than in diabetics without polyneuropathy.[2] Since exact electrodiagnosis of polyneuropathy and CTS is not possible, it is difficult to detect CTS in patients with diabetes.[5]

There are electrophysiological techniques to differentiate CTS in patients with or without neuropathy.[2] However, according to multiple linear regression analyses, there is no significant relationship between the electrodiagnostic and clinical findings of CTS in patients with diabetes.[2,6] The studies conducted on patients with diabetes imply that surgical treatment decisions should be made independently of electrodiagnostic findings.[2,6]

Polyneuropathy in Diabetes

In patients with diabetes, neuropathy is known for its neurological involvement pattern and heterogeneous complications.[7] Diabetic polyneuropathy (DPN) is classified as general, focal (e.g., involvement of the median nerve in CTS), or multifocal (e.g., multiple mononeuropathy; lumbosacral, thoracic, and cervical radiculoplexus neuropathies).[7,8] Any of the above-mentioned neuropathies may occur in patients with diabetes. Histopathological studies indicate lymphocytic infiltration within neuropathic regions, raising the possibility of inflammatory reactions in diabetic neuropathies.[9] However, diabetic sensorimotor polyneuropathy is usually significantly associated with long-term hyperglycemia due to metabolic derangements and microvascular alternations.[10]

Macrovascular and microvascular complications are among the most important and well-documented complications of chronic hyperglycemia in diabetics.[11] The development of diabetic neuropathy is linked to microvascular complications, with a prevalence rate of 50 to 60%.[12] Chronic hyperglycemia causes activation of the plasminogen activator inhibitor-1 (PAI-1) promoter in vascular smooth muscle cells and of transforming growth factor-β (TGF-β) and PAI-1 in arterial endothelial cells. Activation of PAI-1, TGF-α, and TGF-β1 lead to deposition of collagen and formation of extracellular matrix, which may lead to neuroinflammation associated with the vascular component in diabetic neuropathy.[13] Also, activation of the protein kinase C (PKC) pathway in chronic hyperglycemia aggravates oxidative damage and leads to vascular complications.[13]

Neuropathy is associated with decreased nerve function and blood perfusion, malnourished nerves, and nerve injury. Although hyperglycemia is one of the most important pathophysiological factors involved in diabetic neuropathy, it seems that inflammatory responses are also involved (►**Fig. 1**). Oxidative stress and mitochondrial dysfunction damage DNA[14,15] and activate poly (ADP)-ribose polymerase (PARP)[14] and nuclear factor kappa (NF-κ) light-chain enhancer of activated B cells (NF-κB),[14,15] which may cause NAD+/ATP depletion,[14] ultimately leading to nerve disorders. Moreover, inducible nitrite oxide synthase (iNOS), cyclooxygenase 2 (COX-2), interleukin-6 (IL-6), tumor necrosis factor α(TNF-α), and NF-κB, which are potent proinflammatory mediators,[14] propagate immune signaling that in turn leads to diabetic neuropathy.[13,15] Especially NF-κB levels are elevated in peripheral nerves and dorsal root ganglia in experimental

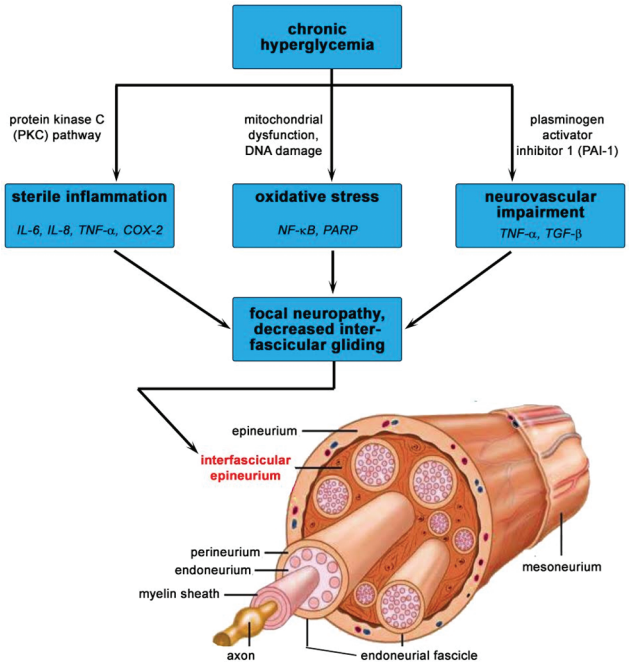

Fig. 1 Summary of the mechanisms involved in median nerve pathology of carpal tunnel syndrome. The relationship between chronic hyperglycemia and oxidative stress, inflammation, and neurovascular impairment have been empirically proven. The bottom part of the figure pertains design based on available evidence, where the interfascicular gliding may be affected by focal neuropathy in diabetic patients. COX-2, cyclooxygenase-2; IL, interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PARP, poly-ADP ribose polymerase; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

diabetic neuropathy.[14,15] Various studies support the role of inflammatory mediators in the development of peripheral neuropathy in diabetic patients, as summarized in ►**Table 1**. Capillary dysfunction due to damage of the capillary circulation pattern may lead to decreased tissue oxygenation and glucose supply. According to Østergaard et al,[14] there is a significant relationship between endoneurial blood circulation and nerve function. Damage to the delicate capillaries of the endoneurium results in tissue hypoxia and increased activity of aldose reductase, both of which play a role in diabetic neuropathy.

Nerve Gliding

Each nervous fiber is surrounded by several layers of connective tissues.[20] These layers included mesoneurium, endoneurium, epineurium, and perineurium which are situated beside each other. The extensibility of these layers plays a crucial role in nerve gliding.[21,22] The nerve gliding is mainly dependent on the integrity of the epineurium layer[21,22] (►**Fig. 1**). Therefore, the accommodation of the epineurium layer relative to its surroundings plays an essential role in the pathogenesis of the nervous injuries.[23] In general, the stretching of the median nerve in the wrist is applied by the epineurium. In normal nerves, this nerve can stretch up to 9.6 mm between full flexion states. However, the stiffen surrounding of the connective tissue can restrict the extensibility of the median nerve; and by causing a shearing force, it can damage or disturb the function of the peripheral

Table 1 Studies supporting the effect of inflammatory factors on the development of neuropathy in diabetic patients

Study	Factors involved	Dysfunction in diabetic patients with neuropathy
Sandireddy et al (2014)[13]	Oxidative stress, IL-6, iNOS, COX-2, TGF-β, PAI-1	Endothelial dysfunction
Østergaard et al (2015)[14]	Oxidative stress, NF-κB, ROS	Capillary dysfunction
Verrotti et al (2014)[16]	Increased oxidative stress, CRP, IL-6, IL-8, TNF-α, endothelin-1	Diabetic autonomic neuropathy
Bilir et al (2016)[17]	Increased proinflammatory response induced elevated concentration of endoglin, apelin, and endocan (may reflect angiogenesis)	Endothelial dysfunction in diabetic peripheral neuropathy
Condorelli et al (2014)[18]	Local inflammatory responses induced MAGI	Diabetic autonomic neuropathy
Vinik et al (2013)[19]	NF-κB, inflammatory cytokines such as TNF-α and IL-6	Diabetic autonomic neuropathy

Abbreviations: COX-2, cyclooxygenase-2; CRP, C-reactive protein; IL, interleukin; iNOS, inducible nitric oxide synthase; MAGI, male accessory gland inflammation or infection; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

nerve.[23] The longitudinal movement of the median nerve in the carpal tunnel is about 9.6 mm at the wrist flexion and 0.7 to 1.4 mm during the wrist extension. Recent findings have shown two types of nerve gliding including total gliding which is related to a specific connective tissue known as the subsynovial connective tissue.[24-26] The complexity of nerve gliding and traction and compression manners were described by Lundborg and Dahlin. According to their theory, a series of events will cause vicious cycling which may result in nerve injury or disturb the extensibility and stretchability of the nerve.[27] Nerves have the capacity to positionally adapt during displacement of surrounding tissues.[28] This locomotor adaptation is provided by the gliding apparatus that surrounds the body of the nerve. Another level of gliding is created by the interfascicular epineurium and facilitates gliding of fascicles against each other.[28] According to clinical observations, disruption of this gliding mechanism contributes to the development and severity of CTS.[29,30] Also based on findings in other studies, nerve gliding dysfunction has main role in median nerve neuropathy.[30-32] The increase of the pressure on the nerve due to the peripheral forces can result in the stiffness of the peripheral nerve. It has been known that in the people suffering from stroke, median nerve compression may occur due to the spasticity in the upper limb and long-term flexion of the wrist. This will disturb the nerve gliding which will be manifested by neuropathy.[32] Histopathological findings have shown edema, fibrosis, demyelination, and Wallerian degeneration among the patients suffering from nerve stiffness due to connective tissue variations, in some specific patients such as those with systemic sclerosis, the peripheral nerve stiffness occurs along with neuropathy due to nerve gliding disturbances.[33]

Median Nerve Elasticity on Ultrasonography

Ultrasonography (US) was first used in CTS in 1992 which was used as a complementary test for pathological investigation of the peripheral nerves.[34] In the US, peripheral nerves have mixed hyperechoic and hypoechoic symptoms; thus the US can be employed as a noninvasive tool to investigate the pathologies of the peripheral nerve pathologies. Elastography ultrasound (EUS) is also a suitable tool for quantitative investigation of the nerve elasticity which has found extensive applications these days.[35,36] Various elastography techniques have been developed such as strain EUS, shear wave EUS (SEUS), acoustic radiation force impulse EUS (ARFI), and transient EUS. Strain EUS is one of the most common ones which is a cost-effective examination-dependent qualitative tool for evaluation of the peripheral nerves.[37] ARFI is an alternative for strain EUS which is not able to estimate the mechanical pressure on the nerve, so it should be classified as a qualitative method.[36,37] Shear wave elastography (SWE) is capable of both qualitative and quantitative nerve investigations with high potentials in assessing the health of nerve and peripheral neuropathy.[29,37] EUS and SWE rely on the biomechanical properties of the peripheral nerve and the elasticity of the tissue which have been employed in the CTS patients. In a study by Miyamoto et al, the median nerve elasticity was significantly different in CTS patients in comparison with normal individuals. Stiffness of the median nerve was 99.7 kPa in these patients, while the normal patients exhibited the stiffness of 32 kPa.[29] Also, they found a higher acoustic coupler/median nerve (AC/MN) strain ratio in the patients.[29] Yoshii et al observed an increased strain ratio in CTS patients versus healthy patients. According to recent findings, median nerve elasticity change is a mechanism involved in the development of CTS.[30]

Interfascicular Gliding Dysfunction and Hyperglycemia

CTS is the most prevalent neuropathy resulting from injury to the median nerve in the wrist.[26,38] There are several studies on diabetes-induced neuropathy, attesting to an essential role of chronic hyperglycemia in the development of this neuropathy. Mitochondrial dysfunction due to increase in intracellular glucose may give rise to inflammatory signaling and oxidative stress.[13,38] Brownlee showed that chronic hyperglycemia augment the reducing equivalents to electron transport chain (ETC) and the electrochemical potential across the inner mitochondrial membrane and hence increases oxidative factors production.[38] At the other hand, microvascular structural variations can result in biochemical damages leading to declining of the endoneurial blood flow

and hence oxygen tension. In diabetic patients, microvascular injuries can cause edema and increase the oxygen supply delay from the capillaries to the nerve cells giving rise to hypoxia.[39] The hypoxia can upregulate various angiogenic factors such as vascular endothelial growth factor (VEGF). An increase in the VEGF was proven in the experimental animal studies on Schwann's cells and neurons. On the other hand, among the diabetic patients, the endoneurial vessels are under the influence of microangiopathic variations which can increment endothelial hypertrophy, hyperplasia basement membrane thickening, and pericyte loss.[39,40] Based on available evidence, decreased nerve elasticity and interfascicular gliding dysfunction due to focal neuropathy affected by biomedical changes contribute to the pathogenesis of CTS in diabetic patients (►**Fig. 1**). The high prevalence of CTS in patients with diabetes and neuropathic comorbidity suggests a common underlying cause that predisposing factors for neuropathy and CTS support this evidence.[34,37] The microvasculature dysfunction and release of inflammatory mediators support the available evidence that these factors affect the median nerve dysfunction by decreased nerve elasticity and interfascicular gliding. According to recent findings, nerve elasticity and its gliding capability are two of the most important factors affecting CTS.[39,40] There are two kinds of gliding: peripheral and interfascicular gliding. Inflammatory damage and microvascular alterations in the interfascicular epineurium of median nerve seem to result in perturbation of the interfascicular gliding mechanism and foster conditions for the development of CTS.[31,39,40]

An increase in proinflammatory signals is observed in both diabetic and healthy patients and a significant relationship exists between increased IL-6 and IL-8 and intercellular adhesion in peripheral nerve in diabetic patients with distal sensorimotor polyneuropathy (DSPN).[15] Nerve biopsies to study molecular biology and immunology are not possible in living people.[28] The first study conducted using animal models indicated stiffer sciatic nerves in rats with diabetes compared to control animals.[41,42] A reduction in blood perfusion of the nerve and a slight increase in pressure around the nerve contributed to the increased nerve stiffness.[43] Sonoelastography is a modern technique to evaluate soft tissue elasticity, and the strain ratio of soft tissue is generally determined using an acoustic coupler.[44] Ishibashi et al demonstrated a significant reduction in nerve elasticity in patients with diabetes in Japan.[44] Biomechanical variations in the nerves of patients with type-II diabetes were also associated with nerve stiffness and a decrease in nerve gliding.[44] Furthermore, high prevalence of CTS in patients with diabetes with neuropathy and decreased nerve gliding observed in radiographic findings support the theory that there is a strong correlation among the degree of sterile inflammation, decrease in nerve elasticity, and diabetic neuropathy.

Diabetic Neuropathy and Results of Carpal Tunnel Syndrome Treatment

Diabetes-induced peripheral neuropathy is associated with debilitating pain and sensory loss, which decreases quality of life. Continuous hyperglycemia increases neuroinflammation and nerve injury, and is ultimately associated with pain and hyperesthesia.[45] Hyperglycemia is a precursor condition of oxidative stress and sterile inflammation. These pathways, which are hyperglycemia-related complications, are associated with nerve injury and developing of neuropathy. Neuropathy may be detected via neurophysiological evaluation.[46-48] However, neurophysiology does not provide useful information about the reason, pathology, or biomechanical variations involved.[44] Both mechanical and physiological events affect the peripheral nervous system.[44] Meanwhile, inflammatory factors, oxidative stress, and hyperglycemia-induced microvascular complications negatively affect peripheral nerves, resulting in pathological sequelae such as decreased peripheral blood perfusion. Chronic hyperglycemia changes the structure of peripheral nerves and imparts a nonreversibility effect,[49] such that an increase in the thickness of peri- and epineurial ensheathment and endoneurial fibrosis were reported in the sural nerves of patients with type-II diabetes mellitus. An increase in fiber thickness of the peripheral nerve sheath is a result of mechanical stresses in patients with diabetes.[50] In animal models, circular pressure in the sciatic nerve of rats with diabetes treated with streptozocin leads to increased stiffness of the sciatic nerve compared to healthy rats. A significant reduction in peripheral blood perfusion of the nerve was observed in these rats.[42] According to Boyd and Dilley, biomechanical variations of the tibial nerve were associated with a reduction in excursion of the ankle. Elasticity changes in the tibial nerve may lead to less excursion of the nerve. There is only one study conducted on nerve elasticity in patients with diabetes, and it indicates a significant reduction in the gliding rate of the tibial nerve.[51]

According to evidence, inflammatory and microvascular factors affect interfascicular gliding of the median nerve in addition to total nerve gliding in the surrounding tissues. Defective interfascicular gliding seems important in patients with diabetes. Taser et al studied fibrosis with thicker and irregular fibers of subsynovial connective tissue and also vascular changes significantly increased in diabetic patients with CTS.[52] The study conducted by Deger et al studied on the role of neoangiogenesis and VEGF in the development of CTS in diabetic patients. They found that increased ischemia-reperfusion damage, neoangiogenesis, and VEGF expression that led to significant neovascularization within the subsynovial connective tissue which has an important impact on CTS occurrence in diabetic patients.[53] However, surgical release of the median nerve leading to a lessening of tunnel pressure was not effective in patients with diabetes with neuropathy. According to Ebrahimzadeh et al, diabetes negatively affects the treatment outcome of carpal tunnel release.[54] Contrary to the findings of Taser et al, decreasing the pressure does not result in improvement of symptoms of median nerve entrapment in patients with diabetes with neuropathy.[52] Zimmerman et al reported that patients with diabetes without neuropathy demonstrated ideal results of surgical release treatment.[55] According to our

theory, decreased elasticity and disorder of the interfascicular gliding in patients with diabetes with neuropathy are important factors in the development of CTS; in this population, symptoms fail to improve despite surgical release and lessening of tunnel pressure.[56] Mozaffarian et al found postsurgery improvement of electrodiagnostic studies in diabetic and nondiabetic patients; however, the difference between pre- and postoperative nerve conduction velocity in diabetic patients and nondiabetic was statistically significant in favor of nondiabetic patients.[56] Also based on Afshar et al Study show that the functional improvement in diabetic CTS patients is similar with the idiopathic cases and the duration of diabetes and its treatment can be related to severity of the disease symptoms after the carpal tunnel releasing surgeries.[57] Lack of an appropriate treatment response to surgery in the case of concurrent neuropathy and CTS also is another evidence. The no-reversibility of nerve disorders in some postsurgical release of carpal tunnel cases may be attributed to nerve injury due to inflammatory mechanisms and microvascular complications. These manifestations impair the interfascicular gliding of the nerves.[39,40,57]

Development of Medical Treatments in Diabetic Patients with Carpal Tunnel Syndrome

Insulin and the insulin-like growth factors (IGFs) may have effective role in the development of the peripheral nervous system.[58] According to experimental studies insulin's effects on neurite formation and neuronal survival were determined in peripheral ganglion cell cultures from chick embryos.[58] Insulin and IGF-II additionally improve survival of sensory and sympathetic neurons.[58] Also IGFs have protecting role on sensory nerve regeneration.[59] Plastino et al showed relation between insulin resistance (IR) and CTS. In 117 patients with moderate-to-sever CTS, the prevalence of glucose metabolism abnormalities was significantly higher.[60] Ozkul et al showed the positive effect of local insulin injection on CTS in diabetic patients which supported this evidence. In this study, treatment with local insulin injection had great potential benefit on improvement of nerve functions in noninsulin-dependent diabetes mellitus(NIDDM), who have mild-to-moderate CTS.[61] Also Greene et al studied the effects of insulin and dietary myoinositol on impaired peripheral motor nerve conduction velocity in diabetic rats. They found that insulin treatment can improve sciatic motor nerve conduction velocity (MNCV).[62] Similarly, interventions aimed at reducing oxidative stress lead to prevented of vascular dysfunction in diabetic patients which may play a role in improving median nerve function.[63]

Antioxidant treatment improves endoneurial oxygenation by correcting neural blood flow. Reactive oxygen species (ROS) cause antioxidant-preventable vascular endothelium abnormalities, neutralizing nitric oxide mediated vasodilation, and increasing reactivity to vasoconstrictors.[63] In study by Cameron and Cotter studied novel drugs, such as ascorbyl-γ-linolenic acid and γ-linolenic acid–lipoic acid, which have effective antioxidant role on nerves' function.[63] In other animal study by Cameron et al evaluated the streptozotocin-diabetic rats were treated with the antioxidant probucol or the prooxidant primaquine in sciatic nerve nutritive endoneurial blood flow.[64] Based on their findings, oxygen-free radical activity has potentially important role in diabetic neuropathy.[64] Of course, the few studies were done on the use of antioxidant agents in improvement of peripheral nerve function in diabetic patients. Di Geronimo et al studied and tried to use of pharmacological treatment (neuroprotection) in patients with CTS and nondiabetic patients, according to their findings, alpha-lipoic acid (ALA) 600 mg/die and gamma-linolenic acid (GLA) 360 mg/die significantly effect on controlling symptoms and improving of functional scores.[65] Also in a meta-analysis and randomized controlled trials study by Mijnhout et al, showed that intravenous administration of ALA leads to significant and clinically relevant improvements of symptomatic peripheral diabetic neuropathy in the short term.[66] In clinical trial study by Boriani et al, the use of ALA in the postoperative period after surgical decompression of the median nerve has been shown to have a significant effect in reducing recurrences and pillar pain.[67] Monroy et al used 600-mg ALA for 1 month before and for 2 months after CTS surgical treatment, leading to improve the clinical and neurophysiologic outcomes after surgery, so that in patients who received ALA in compared with placebo group, none of the participants had positive Phalen's or Tinel's signs at 12 weeks of follow-up; and based on electrophysiological findings, motor and sensory fiber latency and amplitude had significantly improved.[68] Presently, few studies have been conducted on the use of antioxidants for the improvement of peripheral nerve function in diabetic patients. More research in this field is hence warranted

Conclusion

According to the available evidence, there is a relationship between CTS in patients with diabetes and neuropathy. Inflammatory factors, oxidative stress, and microvascular changes negatively affect the function of peripheral nerves, including the median nerve. It seems that increased tunnel pressure and narrowness are not the only factors involved in developing the disease. Decreased nerve elasticity and interfascicular gliding play significant roles in the pathogenesis, such that symptoms of the disease are not improved despite surgical release and reduction of surrounding pressure. Insulin has bioprotective effects on the peripheral nerves against inflammatory factors and neurovascular impairment caused by chronic hyperglycemia. Insulin may be effective in preventing focal neuropathy and interfascicular gliding dysfunction. Also according to recent studied antioxidants, such as ALA, they could theoretically be effective in treating diabetic neuropathy. Therefore, we suggest the concurrent use of antioxidants and pharmacological treatment (neuroprotection) like to ALA with carpal tunnel release in diabetic patients. It seems that can be effective in improving of interfascicular gliding and median neve elasticity.

Conflict of Interest
None declared.

References

1 Bahrmann A, Zieschang T, Neumann T, Hein G, Oster P. [Carpal tunnel syndrome in diabetes mellitus] (in German). Med Klin (Munich) 2010;105(3):150–154
2 Perkins BA, Olaleye D, Bril V. Carpal tunnel syndrome in patients with diabetic polyneuropathy. Diabetes Care 2002;25(3):565–569
3 Thomsen NO, Cederlund RI, Andersson GS, Rosén I, Björk J, Dahlin LB. Carpal tunnel release in patients with diabetes: a 5-year follow-up with matched controls. J Hand Surg Am 2014;39(4):713–720
4 Gül Yurdakul F, Bodur H, Öztop Çakmak Ö, et al. On the severity of carpal tunnel syndrome: diabetes or metabolic syndrome. J Clin Neurol 2015;11(3):234–240
5 Chaudhuri KR, Davidson AR, Morris IM. Limited joint mobility and carpal tunnel syndrome in insulin-dependent diabetes. Br J Rheumatol 1989;28(3):191–194
6 Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology 1993;43(4):817–824
7 Thomas PK. Classification, differential diagnosis, and staging of diabetic peripheral neuropathy. Diabetes 1997;46(suppl 2) :S54–S57
8 Boulton AJM, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. Diabetes Care 2004;27(6):1458–1486
9 Younger DS, Rosoklija G, Hays AP, Trojaborg W, Latov N. Diabetic peripheral neuropathy: a clinicopathologic and immunohistochemical analysis of sural nerve biopsies. Muscle Nerve 1996;19(6):722–727
10 Dyck PJ, Albers JW, Andersen H, et al; Toronto Expert Panel on Diabetic Neuropathy. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev 2011;27(7):620–628
11 Huizinga MM, Peltier A. Painful diabetic neuropathy: a management-centered review. Clin Diabetes 2007;25(1):6–15
12 Vinik AI, Mehrabyan A. Diabetic neuropathies. Med Clin North Am 2004;88(4):947–999, xi
13 Sandireddy R, Yerra VG, Areti A, Komirishetty P, Kumar A. Neuroinflammation and oxidative stress in diabetic neuropathy: futuristic strategies based on these targets. Int J Endocrinol 2014;2014:674987
14 Østergaard L, Finnerup NB, Terkelsen AJ, et al. The effects of capillary dysfunction on oxygen and glucose extraction in diabetic neuropathy. Diabetologia 2015;58(4):666–677
15 Herder C, Bongaerts BW, Rathmann W, et al. Association of subclinical inflammation with polyneuropathy in the older population: KORA F4 study. Diabetes Care 2013;36(11):3663–3670
16 Verrotti A, Prezioso G, Scattoni R, Chiarelli F. Autonomic neuropathy in diabetes mellitus. Front Endocrinol (Lausanne) 2014;5:205
17 Bilir B, Ekiz Bilir B, Yilmaz I, et al. Association of apelin, endoglin and endocan with diabetic peripheral neuropathy in type 2 diabetic patients. Eur Rev Med Pharmacol Sci 2016;20(5):892–898
18 Condorelli RA, Vicari E, Calogero AE. La Vignera S. Male accessory gland inflammation prevalence in type 2 diabetic patients with symptoms possibly reflecting autonomic neuropathy. Asian J Androl 2014;16(5):761–766
19 Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. J Diabetes Investig 2013;4(1):4–18
20 Stolinski C. Structure and composition of the outer connective tissue sheaths of peripheral nerve. J Anat 1995;186(pt 1): 123–130
21 Topp KS, Boyd BS. Structure and biomechanics of peripheral nerves: nerve responses to physical stresses and implications for physical therapist practice. Phys Ther 2006;86(1):92–109
22 Kohrs RT, Zhao C, Sun YL, et al. Tendon fascicle gliding in wild type, heterozygous, and lubricin knockout mice. J Orthop Res 2011;29(3):384–389
23 Aboonq MS. Pathophysiology of carpal tunnel syndrome. Neurosciences (Riyadh) 2015;20(1):4–9
24 Ozkul Y, Sabuncu T, Kocabey Y, Nazligul Y. Outcomes of carpal tunnel release in diabetic and non-diabetic patients. Acta Neurol Scand 2002;106(3):168–172
25 Wehbé MA, Schlegel JM. Nerve gliding exercises for thoracic outlet syndrome. Hand Clin 2004;20(1):51–55, vi
26 Hough AD, Moore AP, Jones MP. Reduced longitudinal excursion of the median nerve in carpal tunnel syndrome. Arch Phys Med Rehabil 2007;88(5):569–576
27 Lundborg G, Dahlin LB. Anatomy, function, and pathophysiology of peripheral nerves and nerve compression. Hand Clin 1996;12(2):185–193
28 Millesi H, Zöch G, Rath T. The gliding apparatus of peripheral nerve and its clinical significance. Ann Chir Main Memb Super 1990;9(2):87–97
29 Miyamoto H, Halpern EJ, Kastlunger M, et al. Carpal tunnel syndrome: diagnosis by means of median nerve elasticity–improved diagnostic accuracy of US with sonoelastography. Radiology 2014;270(2):481–486
30 Yoshii Y, Ishii T, Tanaka T, Tung WL, Sakai S. Detecting median nerve strain changes with cyclic compression apparatus: a comparison of carpal tunnel syndrome patients and healthy controls. Ultrasound Med Biol 2015;41(3):669–674
31 Ogur T, Yakut ZI, Teber MA, et al. Ultrasound elastographic evaluation of the median nerve in pregnant women with carpal tunnel syndrome. Eur Rev Med Pharmacol Sci 2015;19(1):23–30
32 Aslan H, Analan PD. Effects of chronic flexed wrist posture on the elasticity and crosssectional area of the median nerve at the carpal tunnel among chronic stroke patients. Med Ultrason 2018;1(1):71–75
33 Yagci I, Kenis-Coskun O, Ozsoy T, Ozen G, Direskeneli H. Increased stiffness of median nerve in systemic sclerosis. BMC Musculoskelet Disord 2017;18:434
34 Kowalska B, Sudoł-Szopińska I. Normal and sonographic anatomy of selected peripheral nerves. Part I: sonohistology and general principles of examination, following the example of the median nerve. J Ultrason 2012;12(49):120–130
35 Kowalska B, Sudoł-Szopińska I. Ultrasound assessment on selected peripheral nerve pathologies. Part I: entrapment neuropathies of the upper limb - excluding carpal tunnel syndrome. J Ultrason 2012;12(50):307–318
36 Park G-Y, Kwon DR. Application of real-time sonoelastography in musculoskeletal diseases related to physical medicine and rehabilitation. Am J Phys Med Rehabil 2011;90(11):875–886
37 Xiang X, Yan F, Yang Y, et al. Quantitative assessment of healthy skin elasticity: reliability and feasibility of shear wave elastography. Ultrasound Med Biol 2017;43(2):445–452
38 Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005;54(6):1615–1625
39 Dahlin LB. Aspects on pathophysiology of nerve entrapments and nerve compression injuries. Neurosurg Clin N Am 1991;2(1):21–29
40 Samii A, Unger J, Lange W. Vascular endothelial growth factor expression in peripheral nerves and dorsal root ganglia in diabetic neuropathy in rats. Neurosci Lett 1999;262(3):159–162
41 Malik RA, Tesfaye S, Newrick PG, et al. Sural nerve pathology in diabetic patients with minimal but progressive neuropathy. Diabetologia 2005;48(3):578–585

42 Chen RJ, Lin CC, Ju MS. In situ biomechanical properties of normal and diabetic nerves: an efficient quasi-linear viscoelastic approach. J Biomech 2010;43(6):1118–1124
43 Onur MR, Poyraz AK, Ucak EE, Bozgeyik Z, Özercan IH, Ogur E. Semiquantitative strain elastography of liver masses. J Ultrasound Med 2012;31(7):1061–1067
44 Ishibashi F, Taniguchi M, Kojima R, Kawasaki A, Kosaka A, Uetake H. Elasticity of the tibial nerve assessed by sonoelastography was reduced before the development of neuropathy and further deterioration associated with the severity of neuropathy in patients with type 2 diabetes. J Diabetes Investig 2016;7(3):404–412
45 Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab Res Rev 2012;28(Suppl 1) :8–14
46 Misra UK, Kalita J, Nair PP. Diagnostic approach to peripheral neuropathy. Ann Indian Acad Neurol 2008;11(2):89–97
47 Vincent AM, Edwards JL, McLean LL, et al. Mitochondrial biogenesis and fission in axons in cell culture and animal models of diabetic neuropathy. Acta Neuropathol 2010;120(4):477–489
48 Maccarrone M, Brüne B. Redox regulation in acute and chronic inflammation. Cell Death Differ 2009;16(8):1184–1186
49 Dyck PJ, Giannini C. Pathologic alterations in the diabetic neuropathies of humans: a review. J Neuropathol Exp Neurol 1996;55(12):1181–1193
50 Kundalić B, Ugrenović S, Jovanović I, et al. Morphometric analysis of connective tissue sheaths of sural nerve in diabetic and nondiabetic patients. BioMed Res Int 2014;2014:870930
51 Boyd BS, Dilley A. Altered tibial nerve biomechanics in patients with diabetes mellitus. Muscle Nerve 2014;50(2):216–223
52 Taser F, Deger AN, Deger H. Comparative histopathological evaluation of patients with diabetes, hypothyroidism and idiopathic carpal tunnel syndrome. Turk Neurosurg 2017;27(6):991–997
53 Deger AN, Deger H, Taser F. The role of neoangiogenesis and vascular endothelial growth factor in the development of carpal tunnel syndrome in patients with diabetes. Niger J Clin Pract 2016;19(2):189–195
54 Ebrahimzadeh MH, Mashhadinejad H, Moradi A, Kachooei AR. Carpal tunnel release in diabetic and non-diabetic patients. Arch Bone Jt Surg 2013;1(1):23–27
55 Zimmerman M, Dahlin E, Thomsen NO, Andersson GS, Björkman A, Dahlin LB. Outcome after carpal tunnel release: impact of factors related to metabolic syndrome. J Plast Surg Hand Surg 2017;51(3):165–171
56 Mozaffarian K, Owjimehr M, Eskandari Sani B, Mokarami F, Sharifzadeh R. Carpal tunnel release outcomes in diabetic versus non-diabetic patients. Shafa Ortho J 2015;2(2):e1234
57 Afshar A, Tabrizi A, Tajbakhsh M, Navaeifar N. Subjective outcomes of carpal tunnel release in patients with diabetes and patients without diabetes. J Hand Microsurg 2019; doi: 10.1055/s-0039-1697059
58 Recio-Pinto E, Rechler MM, Ishii DN. Effects of insulin, insulin-like growth factor-II, and nerve growth factor on neurite formation and survival in cultured sympathetic and sensory neurons. J Neurosci 1986;6(5):1211–1219
59 Ishii DN, Lupien SB. Insulin-like growth factors protect against diabetic neuropathy: effects on sensory nerve regeneration in rats. J Neurosci Res 1995;40(1):138–144
60 Plastino M, Fava A, Carmela C, et al. Insulin resistance increases risk of carpal tunnel syndrome: a case-control study. J Peripher Nerv Syst 2011;16(3):186–190
61 Ozkul Y, Sabuncu T, Yazgan P, Nazligul Y. Local insulin injection improves median nerve regeneration in NIDDM patients with carpal tunnel syndrome. Eur J Neurol 2001;8(4):329–334
62 Greene DA, De Jesus PV Jr, Winegrad AI. Effects of insulin and dietary myoinositol on impaired peripheral motor nerve conduction velocity in acute streptozotocin diabetes. J Clin Invest 1975;55(6):1326–1336
63 Cameron NE, Cotter MA. Effects of antioxidants on nerve and vascular dysfunction in experimental diabetes. Diabetes Res Clin Pract 1999;45(2,3) :137–146
64 Cameron NE, Cotter MA, Archibald V, Dines KC, Maxfield EK. Anti-oxidant and pro-oxidant effects on nerve conduction velocity, endoneurial blood flow and oxygen tension in non-diabetic and streptozotocin-diabetic rats. Diabetologia 1994;37(5):449–459
65 Di Geronimo G, Caccese AF, Caruso L, Soldati A, Passaretti U. Treatment of carpal tunnel syndrome with alpha-lipoic acid. Eur Rev Med Pharmacol Sci 2009;13(2):133–139
66 Mijnhout GS, Kollen BJ, Alkhalaf A, Kleefstra N, Bilo HJ. Alpha lipoic Acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. Int J Endocrinol 2012;2012:456279
67 Boriani F, Granchi D, Roatti G, Merlini L, Sabattini T, Baldini N. Alpha-lipoic acid after median nerve decompression at the carpal tunnel: a randomized controlled trial. J Hand Surg Am 2017;42(4):236–242
68 Monroy Guízar EA, García Benavides L, Ambriz Plascencia AR, et al. Effect of alpha-lipoic acid on clinical and neurophysiologic recovery of carpal tunnel syndrome: a double-blind, randomized clinical trial. J Med Food 2018;21(5):521–526