TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2013) 43: 831-837
© TÜBİTAK
doi:10.3906/sag-1208-75

Effect of polyneuropathy on development of unilateral diabetic foot ulcer

Fatma Cansel KALEAĞASI[1], Kezban ASLAN[1,*], Hacer BOZDEMİR[1], Bekir Tamer TETİKER[2]
[1]Department of Neurology, Faculty of Medicine, Çukurova University, Adana, Turkey
[2]Department of Internal Medicine, Faculty of Medicine, Çukurova University, Adana, Turkey

Received: 23.08.2012 • **Accepted:** 03.12.2012 • **Published Online:** 26.08.2013 • **Printed:** 20.09.2013

Aim: This study investigates polyneuropathy in patients with unilateral diabetic foot ulcer by using electrophysiological methods and discusses whether electrophysiological parameters are predictive of diabetic foot ulcer development.

Materials and methods: Fifty-two diabetic patients with unilateral diabetic foot ulcers (31 females, 21 males; mean age of 58.5 years) were included in the study.

Results: In the upper extremities, motor fibers were affected in 82% and sensorial fibers were affected in 85% of the subjects. In the lower extremities, motor fibers were affected in 90% of the subjects in the injured site and in 79% of the patients in the intact site, and sensorial fibers were affected in 100% of the patients bilaterally. H-reflex was delayed in 93.2% of the patients at the injured site and in 86.4% of the patients at the intact site. Sensorial fibers were affected more than motor fibers and the condition was more pronounced in the lower extremities.

Conclusion: The electrophysiological data were statistically different between injured and healthy extremities ($P < 0.005$). Our data revealed that nerve conduction studies have an important value in predicting diabetic foot ulcers and even showed that development of ulceration could be prevented in clinically and neurophysiologically documented diabetic neuropathy.

Key words: Unilateral diabetic foot ulcer, polyneuropathy, electrophysiological studies

1. Introduction

Diabetes mellitus is chronic metabolic disease that negatively affects the quality and expectancy of life due to its complications. Foot ulcers secondary to diabetes are a major cause of morbidity and mortality and represent one the most common causes of patients' hospitalization. It is possible to prevent foot ulcers with an appropriate treatment protocol and patient education if the presence of polyneuropathies associated with diabetes is known or if these disorders are diagnosed early (1,2).

The prevalence of peripheral neuropathy has been reported to reach 82% in patients with diabetes mellitus (3). Neuropathy, peripheral vascular disorders, and involvement of somatic nerves as well as autonomic nerves are known to contribute to the development of diabetic foot ulcers (4). At some point in their lives, 15% of diabetic patients may develop foot wounds. Foot ulcerations are an important complication due to high treatment costs and are a major cause of morbidity and mortality, which may be prevented (5–9).

The present study discussed whether nerve conduction velocity is a parameter that is predictive of diabetic foot ulcer development by investigating the presence of polyneuropathy through measurements of motor and sensory nerve conduction velocity values and by comparing the data obtained from the injured and intact sites.

2. Materials and methods

The patients studied had been under follow-up care for diabetes mellitus at the endocrinology clinic of the Çukurova University Faculty of Medicine and had developed unilateral diabetic foot wound complications. Approval of the Ethics Board and informed consent from the subjects were obtained before the study.

Inclusion criteria included absence of any known condition apart from diabetes mellitus that may cause polyneuropathy, no history of wounds in the other foot, and patients who had not undergone amputation for a diabetic foot wound.

Polyneuropathy grading was based on superficial tactile sensation, deep sensation, deep tendon reflexes (DTRs) and muscle force. Effects on 1 or 2 of the considered parameters of DTR, superficial tactile sensation, and

* Correspondence: kezbanaslan@hotmail.com

deep sensation was considered as mild polyneuropathy; effects on all 3 parameters was considered as moderate polyneuropathy; and effects on all 3 parameters plus presence of motor deficit at distal muscles was considered as severe polyneuropathy. Muscle force was assessed over a 5-point scale, where a score of 5 indicates full force and 0 indicates plegia.

Room temperature was controlled at 22 °C and body temperature was controlled at <36 °C during measurements of nerve conduction velocities with Medelec Synergy electromyography. For the electroneurography (ENG) study with superficial electrodes, sensory and motor conduction velocities of the N. medianus and N. ulnaris were evaluated at the right in the upper extremity, and motor conduction velocities of the bilateral N. fibularis and N. tibialis posterior, H-reflex, and N. suralis orthodromic sensory conduction velocities were evaluated in the lower extremity.

A visual analog scale (VAS) was used for pain threshold, for which a score of 10 indicates the most severe pain and 0 indicates no pain (VAS scores: 10–8 severe pain, 7–4 moderate pain, 3–1 mild pain) (10).

Localization and diameter of the diabetic foot wound and its duration were noted. The most severe wounds were given a grade of 5 and the mildest wounds were given a grade of 1 according to the Wagner classification system (11).

Data were analyzed using SPSS 14.0. The chi-square test was used for intergroup comparisons of noncontinuous variables, and McNemar's test was used to adjust the findings obtained from the wounded and intact sites. Intergroup comparison of measurements was carried out using the Wilcoxon test while Spearman's correlation test was used for correlation analyses. Statistical significance was set at $P < 0.05$.

3. Results

A total of 52 patients, 31 females (59.6%) and 21 (40.4%) males, being followed-up for unilateral diabetic foot wound were included in the study. Mean period of diabetes mellitus was 14 years. Mean age was 59 (range: 24–83) for the female subjects and 58 (range: 36–75) for the male subjects. Body mass index (BMI) was 27.6 (range: 18–40) in females and 25 (range: 19–35) in males (Table 1). Comparison of female and male subjects by age group did not yield statistically significant differences in terms of BMI and diabetes mellitus periods ($P = 0.1$ and 0.8, respectively).

Wound duration was 115 (range: 3–1080) days and wound diameter was 17.6 (range: 2–130) cm on average. Wound severity was 2.1 (range: 1–4) on average according to Wagner classification. There were 15 (28.8%) subjects with a Wagner grade of 1, 19 subjects with grade 2 (36.5%), 13 subjects with grade 3 (13.25%), and 5 subjects with grade 4 (9.6%). Pain threshold as assessed by the VAS had a mean score of 5.7 (range: 0–10) (Table 1). As the Table 1 demonstrates, 19% of the subjects had no pain complaints but 7.6% of the subjects had mild pain symptoms, while moderate and severe pain was noted for 46.2% and 26.9% of the patients, respectively. Fasting blood glucose level was 230 mg/dL on average. HbA1c was 9.6 mg/dL on average (Table 1).

Wounds associated with diabetes were in the right foot in 27 (52%) and in the left foot in 25 (48%) of the subjects. Twelve patients (23%) had 2 diabetic foot wounds in the same feet and the remaining 40 patients (77%) had a single wound.

The subjects' neurological examinations revealed the following: deep tendon reflexes were abolic in 40 (76.9%) subjects and hypoactive in 6 (11.5%) subjects, for a total of 46 subjects (88.4%) with either areflexia or hyporeflexia. Deep sensation involvement was noted in 51 subjects (98%). Hypoesthesia at distal extremities was identified in 47 subjects (90%). Mild polyneuropathy in 3 subjects, moderate polyneuropathy in 20 subjects, and severe polyneuropathy in 29 subjects were verified based on the findings of neurological examinations. It is noteworthy that more than half of the subjects (55.7%) had severe polyneuropathy.

Table 1. Subjects' demographical and biochemical data.

	Mean ± SD	Min–max
Age (years)	58.3 ± 11.2	24–83
Disease period (years)	13.4 ± 7.4	0–30
BMI (kg/m^2)	26.75 ± 5.2	19–40
Wound duration (months)	115 ± 180	3–1080
Wound diameter (cm)	17.6 ± 24.5	2–130
VAS score	5.7 ± 3.2	0–10
Wagner score	2.1 ± 0.9	1–4
C-reactive protein	51 ± 56	3.1–238
Sedimentation	44 ± 26	2–116
Blood urea nitrogen	23 ± 12	7–72
Fasting blood glucose	230 ± 103	87–582
HbA1c	9.6 ± 2.6	5.8–18
Low-density lipoprotein	97 ± 31	42–172
Triglycerides	164 ± 115	53–636
Leukocytes	10.8 ± 5.3	4.8–29.3

3.1. Electroneurography findings

The sensory branch of the median nerve could not be stimulated in 29 (55%) of the subjects and deceleration in the sensory conduction velocity was observed in 19 (36.5%) subjects, resulting in a total of 48 (92.3%) subjects with sensory involvement. The motor branch of the median nerve could not be stimulated in 1 (1.9%) subject and was found decelerated in 43 (80%) subjects, resulting in a total of 44 (84.6 %) patients with median nerve motor branch involvement. The sensory branch of the ulnar nerve could not be stimulated in 16 (30.7%) subjects and 28 (54%) had slowed conduction velocity. Motor conduction velocity was slowed in 30 (58%) subjects. A combined assessment of median and ulnar nerve findings showed that sensory involvement was more frequent (Table 2).

The fibular nerve could not be stimulated in 29 subjects (56.7%) in the foot with the diabetic wound and in 12 subjects (23%) in the healthy foot. Motor conduction velocity was decreased in 18 subjects (35%) in the wounded foot and in 29 subjects (56%) in the healthy foot. Overall, the fibular nerve was affected in 47 subjects (90.3%) in the wounded site and in 41 patients (78.8%) in the intact site (P = 0.005, Table 3; P = 0.01, Table 4). The motor branch of the posterior tibial nerve could not be stimulated in 28 subjects (53.5 %) in the wounded site and conduction velocity was decreased in 18 (35%) subjects. This nerve could not be stimulated in the intact site in 11 (21%) subjects, while the motor conduction velocity was decreased in 28 (53%) patients (Tables 2 and 3; P = 0.001 for Table 3). Nerve conductions had a decreased

Table 2. Electroneurography findings (N: Nervus, dl: distal latency, cv: conduction velocity, PTN: posterior tibial nerve).

		No response		Prolonged latency		Normal response	
		n	%	n	%	n	%
N. medianus motor dl.		1	1.9	3	65	17	33
N. ulnaris motor dl		0	0	1	27	38	73
N. fibularis distal latency	Wounded	29	56	1	23	11	21
	Intact	12	23	22	42	18	35
PTN distal latency	Wounded	28	53	6	11	18	35
	Intact	11	21	5	10	36	69
		No response		Slow conduction		Normal response	
		n	%	n	%	n	%
N. medianus motor cv.		1	1.9	42	80	9	18
N. medianus sensory cv.		29	55	1	36.36	4	15.4
N. ulnaris motor cv.		0	0	3	58	22	42
N. ulnaris sensory cv.		16	30.7	28	54	8	15.3
N. fibularis cv	Wounded	29	55	18	35	5	10
	Intact	12	23.1	29	56.7	11	21.2
PTN cv.	Wounded	28	53.3	18	35	6	11.5
	Intact	11	21	28	54	13	25
N. suralis cv.	Wounded	48	92.3	4	7.7	0	0
	Intact	48	92.3	4	7.7	0	0
		No response		Delayed conduction		Normal response	
		n	%	n	%	n	%
H-reflex	Wounded	37	71	11	21.1	4	7.7
	Intact	26	50	19	36.5	7	13.6

Table 3. Electroneurography findings of the lower extremity; mean values represent only those where stimulation could be achieved (N: Nervus, lat: latency).

		Wounded side n Mean (min–max)	Intact side n Mean (min–max)	P
N. fibularis	Distal lat. (ms)	(n = 23) 6.4 (4.6–11.7)	(n = 41) 6.7 (3.9–12.9)	0.005
	Conduct. velocity (m/s)	(n = 23) 36.7 (16.6–52.5)	(n = 41) 36.1 (14.8–52.3)	0.003
N. tibialis posterior	Distal lat. (ms)	(n = 24) 6.5 (4.3–11.0)	(n = 41) 6.1 (4.2–8.3)	0.001
	Conduct. velocity (m/s)	(n = 24) 35.3 (16.6–43.4)	(n = 41) 37.3 (23.5–51.0)	0.005
H-reflex	(ms)	(n = 15) 35.5 (26.9–46.0)	(n = 26) 36.4 (27.6–48.0)	0.002
N. suralis	Conduct. velocity (m/s)	(n = 4) 33.3 (29.0–35.0)	(n = 4) 38.9 (30.2–37.0)	0.893

velocity and could not be stimulated in the foot with the diabetic foot ulcer. Fibular nerve involvement was more pronounced, although it was not significant (Tables 3 and 4).

H-reflex was abnormal in 48 subjects (92.3%) in the wounded foot (it could not be measured in 37 subjects (71%) and was delayed in 11 subjects (21.2%)). Lack of response of delay was noted in 45 subjects in the intact foot (it could not be measured in 26 subjects (50%) and was delayed in 19 subjects (36.5%)). H-reflex in the intact foot was statistically significantly more affected (P = 0.002, Table 3).

Sensory action potential of the sural nerve could not be measured in 48 subjects (92.3%) both in the wounded and intact sides. Conduction velocity was decreased in 4 patients for whom nerve stimulation could be achieved. Overall, the findings show that the sural nerve was affected equally on both sides in all subjects, and that sensory involvement was bilaterally symmetric or similar in the lower extremity (Table 2).

The fibular nerve, posterior tibial nerve and sural nerve distal latencies, nerve conduction velocities and H-reflexes in the wounded and intact sides of the lower extremity were compared. Failure to stimulate nerves was associated with the severity of polyneuropathy. Although the mean value for fibular nerve distal latency was longer in the intact side compared to the wounded side, a statistically significant delay was determined for the wounded side compared to the intact side when the nonstimulated values were taken into account (P = 0.01 and 0.006, Table 4).

The mean value of the posterior tibial nerve conduction velocity was decreased in the wounded side (P = 0.005). The mean value for H-reflex was delayed to a higher extent in the intact side but was significantly more delayed in the wounded side when the nonstimulated values were taken into account (P = 0.002). The sural nerve could be stimulated on both sides only in 4 subjects for each, while no meaningful bilateral response could be obtained from the remaining 48 subjects. Although the mean sural nerve conduction velocity was higher in the intact side, the difference was not statistically significant (P = 0.893) (Table 3).

Polyneuropathy was mild in 3 subjects (5.76%), moderate in 20 subjects (38.5%), and severe in 29 subjects (55.74%). Comparison of the degree of polyneuropathy and ENG findings showed that nerves could be stimulated to a lesser extent in the presence of severe polyneuropathy. Distal latencies of the motor branches of median and ulnar nerves increased and motor and sensory conduction velocities decreased in parallel with the degree of polyneuropathy. However, the only statistically significant difference was noted for the median nerve's motor conduction velocity. The fibular and posterior tibial nerves' distal latencies increased, and H-reflex was delayed in parallel with the severity of polyneuropathy. The difference was statistically significant (Table 4).

4. Discussion

Peripheral neuropathy has been described as a strong risk factor for foot ulceration in many studies and reported in more than 80% of the affected individuals. A common finding of several investigators is that decreases in or loss of deep tendon reflex, decreased monofilament pressure sensation, decreased vibration sensation, muscle

Table 4. Relationship between the upper extremity nerve conduction values and degree of polyneuropathy (N: Nervus, Av: average).

	Wounded side polyneuropathy grade						P	Intact side polyneuropathy grade						P
	Mild		Moderate		Severe			Mild		Moderate		Severe		
	n	Av	n	Av	n	Av		n	Av	n	Av	n	Av	
N. fibularis														
Distal latency (ms)	3	5.1	13	6.2	7	7.2	0.001	3	5.3	17	5.9	22	7.5	0.01
Conduction velocity (m/s)	3	7.4	13	36.1	7	34.0	0.001	3	44.7	17	37.4	22	35.3	0.063
N. tibialis posterior														
Distal latency (ms)	3	5.0	13	6.3	8	6.8	0.003	3	4.6	17	6.0	21	6.4	0.006
Conduction velocity (m/s)	3	41.2	13	33.7	8	33.6	0.002	3	43.5	17	37.0	21	36.4	0.029
H-reflex (ms)	3	29.8	4	34.9	8	37.8	0.002	3	31.4	13	36.8	10	37.2	0.007
N. suralis														
(m/s)	2	4.7	2	32.0	0	0	0.001	2	32.4	2	43.3	0	0	0.001

weakness, poor glycemic control, decrease joint mobility, and low high-density lipoprotein levels were predisposing factors for ulcer development (1,3,5,6). Moreover, ulcer development and lower extremity amputations have been reported to be more frequent among males, patients with a disease history of 10 years or more, and those with poor glycemic control and cardiovascular or retinal or renal complications (12,13). The incidence of foot ulceration in diabetic patients as 7.2%–18% has also been reported (5,14). No statistically significant difference was noted between the demographical characteristics of male and female subjects of the present study. Twelve patients (23%) had 2 diabetic foot wounds in the same feet and the remaining 40 patients (77%) had a single wound. The long wound duration noted in the present study may be due to the fact that our hospital was the reference hospital of the region, and the referral chain may have prolonged patients' presentation to the hospital.

Polyneuropathy severity grading based on the Michigan diabetic polyneuropathy score (5) showed normal examination findings in none of the subjects, while more than half of them (55.7%) had findings of severe polyneuropathy, 20 (38%) had moderate polyneuropathy, and 3 (5.7%) had mild polyneuropathy findings. Glycemic control was poor in the subjects of the present study, similar to the findings of Peters et al. (15).

Several studies have reported a prevalence of peripheral neuropathy in patients with diabetes mellitus, ranging between 5% and 90% (16). Rota et al. determined electrophysiological involvement in 82% of their subjects, of whom 62.2% had multiple nerve involvement (3). Fedele et al. reported a diabetic neuropathy frequency of 32.3% (17). In the present study, all subjects but one (98%) had dysfunction in multiple parameters in the lower and upper extremities as determined through electrophysiological methods. Polyneuropathy was determined electrophysiologically in all patients (100%), with one patient having only a decreased sural nerve conduction velocity. All our subjects were diagnosed with diabetic sensorimotor polyneuropathy according to the relevant criteria of the American Academy of Neurology (Table 2) (18).

Nerve conduction studies have demonstrated that the median nerve branch is affected with a frequency of 92% (48 subjects), while the motor branch is affected with a frequency of 82.6% (43 subjects), with sensory involvement being more frequent. An overall analysis of the median and ulnar nerves showed that the sensory branches were more affected in both nerves and that this was more marked in the median nerve (Table 2) (3).

In our study, the fibular nerve and tibial nerve were markedly more affected in the wounded side compared to the intact side (Tables 3 and 4). An evaluation of motor conduction velocity in active nerves showed that more patients had decreases in conduction velocity in the intact side due to the lesser number of stimulated nerves in the wounded side. When the fibular and posterior tibial nerves were assessed together, the number of stimulated posterior tibial nerves was less in diabetic patients, i.e. this nerve was affected to a higher extent. When assessed with electrophysiological methods, the diabetic foot wound was more frequent in the side where polyneuropathy was more severe.

Comparison of rates between wounded and intact sides in our subjects showed that H-reflex was more frequent in the wounded side and the difference was noted to be statistically significant (Table 3). This also suggests that H-reflex may predict diabetic foot ulcer development in the presence of neuropathy.

Our study showed that motor nerves in the lower extremity could not be stimulated to any extent in 56% of the subjects, and lack of stimulation was more common in the wounded side. Nerve conduction velocities in the lower extremity were affected with a rate of 90% and sensory fibers were affected 100%. In the upper extremity, motor fibers and sensory fibers were affected in 82% and 85%, respectively (Table 2). Sensory fibers were affected to a higher extent compared to motor fibers and this effect was more pronounced in the lower extremity. This finding supports the opinion that peripheral neuropathy is more pronounced in the lower extremity (19,20).

Comparison of conduction velocity and other parameters in all nerves studies in the wounded and intact sides showed that effects in the wounded side were more marked compared to the intact side and the difference was, again, significant (Tables 3 and 4) ($P < 0.05$). Given these findings, we are of the opinion that the risk of ulcer development would be higher in the site where electrophysiological effects are more evident, although the presence of diabetic polyneuropathy has been shown to constitute a risk factor for foot ulceration and neuropathy has been reported to be bilateral by electrophysiological methods. However, as was described before, sural nerve parameters were excluded from the analyses due to the lack of adequate data. There are currently no studies in the literature comparing nerve conduction values in the wounded and intact sides in patients with unilateral diabetic foot ulcer, or discussion of whether asymmetric involvement predisposes patients to unilateral ulceration. On the other hand, planar immunoscintigraphy serves as an effective diagnostic tool for precise localization of infection (21). Decreased fibular nerve conduction velocity was shown to be the most predictive parameter for new foot ulceration in a 6-year follow-up study, while other nerve conduction parameters in the lower extremity were not discussed (22). Although diabetic polyneuropathy is known to be symmetric, our finding showing that one site could be more affected electrophysiologically is a first to the best of our knowledge. Earlier ulcer development in the more affected side may be due to muscle weakness associated with the severity of neuropathy in intrinsic muscles and secondary foot deformities.

Parallelism between clinical polyneuropathy findings and electrophysiological effects is consistent with the literature. Similar to previous research, our studies have determined a relationship between neurologic disability scores and nerve conduction values (23,24). Our study has also shown that sensory and autonomous neuropathies usually progress as the diabetes period prolongs, which is also consistent with the literature (25).

However, since coarse fibers are affected in diabetic polyneuropathy, it was not surprising to detect a correlation between nerve conduction values and the degree of pain symptom, which is a sign of thin fiber involvement (26).

While no correlation between wound size and nerve conduction velocity was noted, an increased latency in fibular distal latency and slowed posterior tibial nerve conduction velocity was observed in the wounded side with increased Wagner grade. This may be due to the fact that the depth rather than size of the wound is taken into consideration in the Wagner qualification system. The fibular nerve was noted to be affected to a higher extent than the posterior tibial nerve from the Wagner grade. The fibular nerve was more affected than the posterior tibial nerve in terms of nerve conduction. This may be associated with the fact that the fibular nerve stem is located more proximally and is longer than the tibial nerve.

Van Schie et al. determined decreased peroneal nerve conduction, particularly in the tibial nerve, with increased muscle weakness in groups with a history of diabetic neuropathy or diabetic foot ulcer, and described that this might be an independent risk factor for development of foot ulcer development (23). Comparison of muscle strength and ENG findings in our subjects demonstrated a decreased nerve conduction velocity and increased distal latency depending on the degree of muscle weakness and clinical severity of polyneuropathy. Andreassen et al. reported findings supportive of our results (27). Our study showed correlations between muscle weakness and H-reflex and sural nerve conduction velocity as well as motor conduction velocity. However, this relation was not statistically significant. This may be due to the limited number of patients with muscle weakness.

Our study demonstrated that the side that is identified to be more affected by electroneurography is more predisposed to ulcer development. Although diabetic polyneuropathy is known to be symmetric, our finding showing that one site could be more affected electrophysiologically is a first to the best of our knowledge. Earlier ulcer development in the more affected side may be due to muscle weakness associated with the severity of neuropathy in intrinsic muscles and secondary foot deformities. Therefore, values obtained from both lower extremities should be compared in standard electrophysiological analysis of diabetic sensorimotor polyneuropathy. Moreover, protective measures should be taken to prevent ulcer development in the more affected side (2,27).

References

1. Litzelman DK, Marriott DJ, Vinicor F. Independent physiological predictors of foot lesions in patients with NIDDM. Diabetes Care 1997; 20: 1273–8.
2. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005; 293: 217–28.
3. Rota E, Quadri R, Fanti E, Isoardo G, Poglio F, Tavella A et al. Electrophysiological findings of peripheral neuropathy in newly diagnosed type II diabetes mellitus. J Peripher Nerv Syst 2005; 10: 348–53.
4. Özge A, Saraçoğlu M, Gürtekin Y, Erenoğlu NY, Akyatan MN. The sensitivity of sympathetic skin responses and standard electrophysiological methods in diagnosis of diabetic neuropathy. Electromyogr Clin Neurophysiol 2000; 40: 37–43.
5. Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJM. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. Diabetes Care 1998; 21: 1071–75.
6. Boulton AJM. The diabetic foot. In: Gries A, Cameron N, Low AP, Ziegler D, Anderson H, Arezzo JC et al., editors. Textbook of Diabetic Neuropathy. Stuttgart: Thieme; 2003. p.295–305.
7. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. Diabetes Care 2000; 23: 606–11.
8. Gergg EW, Sorlie P. Prevalence of lower extremity disease with and without diabetes. Diabetes Care 2004; 27: 1591–8.
9. Bild DE, Selby JV, Sinnock P, Browner WS, Braveman P, Showstack JA. Lower extremity amputation in people with diabetes. Epidemiology and prevention. Diabetes Care 1989; 12: 24–7.
10. Bellamy N. Principles of outcome assessment. In: Hochberg M, Silman A, Smolen J, Winblat M, Weisman M, editors. Rheumatology, 3rd ed. Toronto: Mosby; 2003. p.21–31.
11. O'Neal LW, Wagner FW. The Diabetic Foot. St Louis (MO): Mosby; 1983.
12. National Diabetes Data Group. Diabetes in America. Bethesda (MD): Department of Health and Human Services; 1995.
13. Demir S, Öğe A, Karaahmetoğlu S, Müftüoğlu O, Naldöken S. Diabetic osteopathy: who is at risk? Turk J Med Sci 2001; 31: 255–60.
14. Crawford F, Inkster M, Kleijnen J, Fahey T. Predicting foot ulcers in patients with diabetes: a systematic review and meta-analysis. QJM 2007; 100: 65–86.
15. Peters EJG, Lavery LA. Effectiveness of the diabetic foot risk classification system of the international working group on diabetic foot. Diabetes Care 2001; 24: 1442–7.
16. Dyck PJ. Detection, characterization and staging of polyneuropathy in diabetics. Muscle Nerve 1988; 11: 21–32.
17. Fedele D, Comi G, Coscelli C, Cucinotta D, Feldman EL, Ghirlanda G et al. A multicenter study on the prevalence of diabetic neuropathy in Italy. Italian Diabetic Neuropathy Committee. Diabetes Care 1997; 20: 836–43.
18. England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2005; 64: 199–207.
19. Boulton AJM, Malik RA. Diabetic neuropathy. Prevention and treatment of diabetes and its complications. Med Clin North Am 1998; 82: 909–29.
20. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R et al. Diabetic Neuropathies. a statement by the American Diabetes Association. Diabetes Care 2005; 28: 956–62.
21. Bohchelian H, Klisarova AD, Koeva LA. Radioimmune imaging of diabetic foot infection - Tc-99m-labelled antigranulocyte antibody in combination with tc-99m-methylene diphosphonate bone scintigraphy. Turk J Med Sci 2002; 32: 255–9.
22. Carrington AL, Shaw JE, Van Schie CHM, Abbott CA, Vileikyte L, Boulton AJM. Can motor nerve conduction velocity predict foot problems in diabetic subjects over a 6-year outcome period? Diabetes Care 2002; 25: 2010–15.
23. Van Schie CHM, Vermigli C, Carrington AL, Boulton A. Muscle weakness and foot deformities in diabetes. Relationship to neuropathy and foot ulceration in Caucasian diabetic men. Diabetes Care 2004; 27: 1668–73.
24. Baba M, Ozaki I. Electrophysiological changes in diabetic neuropathy: from subclinical alterations to disabling abnormalities. Arch Physiol Biochem 2001; 109: 234–40.
25. Kihara M, Mitsui M, Nishikawa S, Nishimoto K, Takahashi M. Comparison of electrophysiologic and autonomic tests in sensory diabetic neuropathy. Clin Auton Res 1998; 8: 213–20.
26. Schüller TB, Hermann K, Baron R. Quantitative assessment and correlation of sympathetic, parasympathetic, and afferent small fiber function in peripheral neuropathy. J Neurol 2000; 247: 267–72.
27. Andreassen CS, Jakobsen J, Andersen H. A progressive late complication in diabetic distal symmetric polyneuropathy. Diabetes Care 2006; 55: 806–12.